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Original Communications

CERTAIN EFFECTS OF HEMOPHILIA ON THE GROWING SKELETON

SOME ROENTGENOGRAPHIC OBSERVATIONS ON OVERGROWTH AND DYSGENESIS OF THE EPIPHYSES ASSOCIATED WITH CHRONIC HEMARTHROSIS

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BLEEDING into the joints is a frequent and distressing complication of hemophilia. In 1897 Shaw reported the first roentgenographic findings in knee and elbow of a patient 30 years of age. Since then the hemophilic arthropathies in adolescents and adults have been studied by several investigators,[2] and many of the anatomic and roentgen features of the lesions in the bones and soft tissues are well known. The majority of bleeders who have hemarthrosis develop the articular changes prior to adolescence, as shown in Thomas' study,[3] in which 89 per cent of 98 hemophilic patients with hemarthrosis developed clinical evidence of joint involvement before they reached the age of 10 years; in one case hemarthrosis of the ankle occurred in the third month of life. Notwithstanding, there have been only a few roentgen studies of hemophilic joints in preadolescence when the epiphyses are growing and differentiating rapidly.

In the American literature we have found records of roentgenographic examinations of hemophilic joints in two children younger than 10 years. In 1919 Wilson[4] pointed out that epiphyseal maturation is accelerated in hemophilic hemarthrosis; she reported the findings in the elbow of a boy 9 years of age. Seven years later Doub and Davidson[5] described the roentgen changes in a boy 6 years of age. In the standard pediatric texts and systems of pediatrics the modification in the development of the epiphyses present in hemophilic hemarthrosis receives no mention, although all authors agree on the frequency and serious prognosis of the articular lesions. In their text on roentgenographic interpretation Holmes and Ruggles[6] state that squaring and enlargement of the epiphyses may be present, and in Ferguson's recent volume[7] on the roentgen diagnosis of diseases of

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the extremities and the spine there is an illustration of advanced maturation of the epiphyses at the elbow which resulted from previous hemophilic bleeding into this joint.

In the foreign periodicals Klason[8] found precocious development of the trochlea and capitellum of the humerus in the hemophilic elbow of a boy 11 years of age. Escande and Tapie[9] noted hypertrophy of the patella in a boy 9 years of age, with a hemarthrotic knee. Montanari,[10] Peterson,[11] and Lohr[12] described three patients aged 2, 11, and 6 years, respectively, with hemophilic hemarthrosis of the hip joint and coxa plana resembling Perthes' disease. In the German roentgenologic texts of Assmann[13] and of Becker[14] no mention is made of the epiphyseal changes in hemophilic joints. The most complete discussion of the roentgen features of the epiphyses in hemophilic hemarthrosis is that given in Brailsford's *Radiology of Bones and Joints*.[15] He states that epiphyseal ossification is disturbed and that roentgenograms sometimes show a fragmented appearance of the epiphyses as in osteochondritis; and that, if the bleeding occurs into the hip joints in young persons, the femoral head may show changes comparable with those seen in Perthes' disease.

In summary, precocious ossification of the epiphyses in hemophilic involvement of the growing skeleton has been specifically described in three children aged 4, 7, and 8 years, and enlargement of the epiphyses has been noted in several other instances. Irregular and asymmetrical ossification of the epiphyses in preadolescents has been reported in the hip joint in three cases.[10, 11, 12]

The subject of this report is the disturbed development of the epiphyses in five children selected from a group of eleven juvenile hemophiliacs with joint involvement. In all five the development of the epiphyses is advanced, and dysgenesis is present in the capitulum of the radius in two cases and in the proximal epiphysis of the femur in one case. In addition, the roentgen features produced by intra-articular, intraosseous, and subperiosteal hemorrhages are presented.

CASE 1.—*Accelerated maturation of the epiphyses at knee and elbow after recurrent hemarthroses.*

M. H. (B. H. 325186), male, was admitted at the age of 4 years with a painful swelling of the left knee which had been present for three months. There were no known bleeders in the family. The first hemorrhage occurred in the sixth month of life when he bled for fifteen hours after a slight injury to the lips. A few weeks later he bled excessively from a small cut in the finger, and thereafter bleeding into the skin occurred repeatedly after trivial trauma. At 2 years of age there were severe hemorrhages during and after mastoidectomy, and ten months later he was in bed for five weeks because of bleeding into the ankle joint. Injury of the left knee at 3 years, 9 months of age was followed by local pain and swelling which had persisted for three months when he was first seen. On physical examination he proved to be a poorly developed, pale boy with tender, painful

swelling and some limitation of motion of the left knee. The clotting time was 13 minutes (capillary method); the bleeding time two minutes; there were 770,000 blood platelets per cubic millimeter. After three weeks of rest in bed with the left lower extremity in a splint, the local swelling of the knee subsided.

He returned twice during the next year because of hemorrhages in the left knee, and at approximately five years of age the swelling of the knee became permanent. When he was 7 years, 3 months old the lower extremity was held in continuous flexion at the knee with almost complete ankylosis of this joint.

The roentgenographic findings at this time, three and one-half years after the initial involvement of the left knee, are shown in Fig. 1. The soft tissues both within and without the joint show an irregular increase in opacity which approaches calcium density in some areas. All of the bones show severe osteoporosis which, however, is more marked in the epiphyses than in the diaphyses. In both the femoral and tibial epiphyses there are several cystlike oval areas of diminished density surrounded by annular linear shadows of increased density. The largest of these, 20 by 25 by 10 mm., is situated in the tibial epiphysis just below the intercondylar spines. The intercondylar fossa of the femur is widened and deepened, and the articular facets of the tibia are deepened, particularly the medial facet. The articular borders of the bones are irregularly serrated, more markedly on their medial aspects. The joint space is considerably reduced at its periphery.

In addition to these changes, the epiphyses are larger and more completely differentiated on the hemarthrotic side. Accelerated epiphyseal maturation is well demonstrated in the left tibial epiphysis where the intercondylar spines are readily seen while they can be barely made out in the right tibia. The measurements were as follows (all measurements represent in millimeters the largest diameter of each axis):

	Left	Right
Femurs		
Epiphyses		
Transverse axes	65	59
Anteroposterior axes	49	35
Depth of intercondylar fossae	16	9
Lateral condyle (vertical axes)	30	25
Medial condyle (vertical axes)	35	24
Shafts		
Transverse axes	59	57
Anteroposterior axes	30	33
Tibias		
Epiphyses		
Transverse axes	55	50
Anteroposterior axes	39	32
Vertical axes	17	15
Shafts		
Transverse axes	46	48
Anteroposterior axes	34	33
Patellas		
Anteroposterior axes	13	7
Vertical axes	24	18

These measurements show that all of the epiphyses on the left are larger than their counterparts on the right. It is doubtful if the difference in the measurements of the shafts on the two sides is significant. The left fibula and its epiphysis show marked rarefaction and irregularity of the superior epiphyseal margins. Measurements of the epiphyses of the fibulas on the two sides are practically identical.

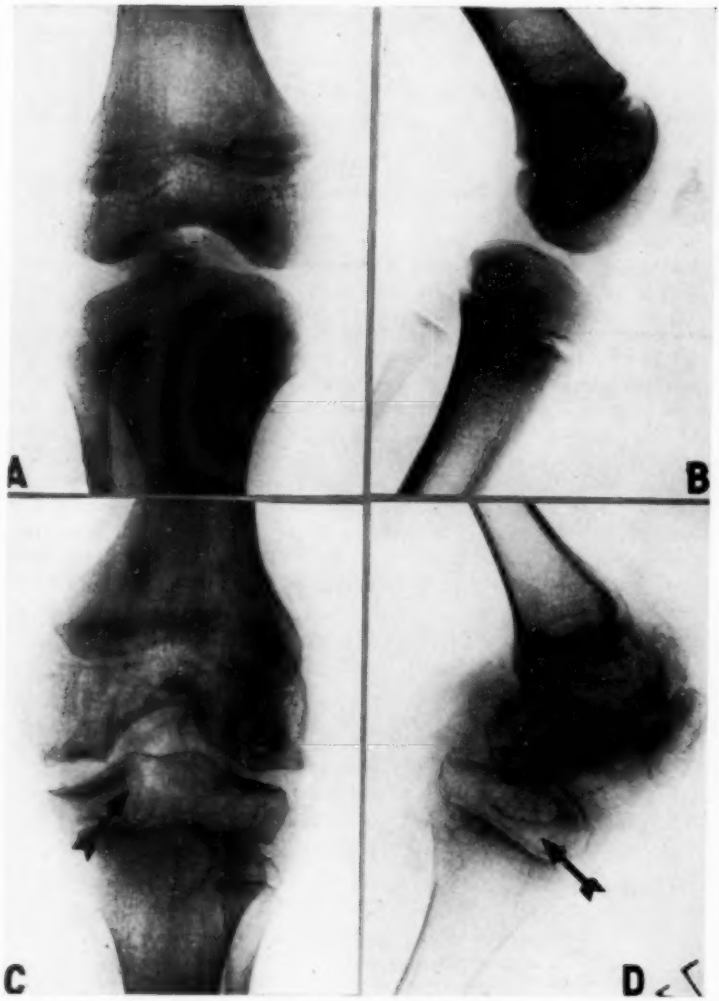

Fig. 1.—Case 1. Overgrowth and accelerated development of the epiphyses in chronic recurrent hemarthrosis of the knee.

A and *B*, Frontal and lateral projections of normal right knee.

C and *D*, Frontal and lateral projections of hemarthrotic left knee. There is marked increase in the density of the soft tissue due to the deposition of iron, and there is a diffuse demineralization of all of the bones which is more marked in the epiphyses than in the shafts. Note in *C* the irregular erosion of the articular surfaces of the medial halves of the femur and the tibia. The intercondyloid fossa is deepened and widened. Opposite the arrow points in *C*, *C'*, *D* and *D'* there is a large cystic area with sharply demarcated borders, the so-called "blood cyst" produced by intraosseous hemorrhage. Overgrowth of the epiphyses and the patella is evident in their greater size on this side, and the increased differentiation is seen in the more completely developed intercondylar spines and the articular facets of the tibial epiphyses.

The left elbow had been the site of recurrent hemarthroses for several years. The date of the initial hemorrhage into this joint was not known. The roentgenographic changes in the elbows when the patient was 10 years, 8 months of age, are shown in Fig. 2. In the left elbow accelerated maturation of the epiphyses is well shown by the increased size of the capitulum of the radius and the capitellum of the humerus and by the presence of ossification centers in the olecranon of the left ulna and trochlea of the left humerus, although neither of the latter two ossification centers are present on the right. The measurements of the bones of the elbow joint were as follows:

Radii	Left	Right
Shafts		
Transverse axes	17	13
Anteroposterior axes	16	14
Capitulums		
Transverse axes	17	13
Anteroposterior axes	16	12

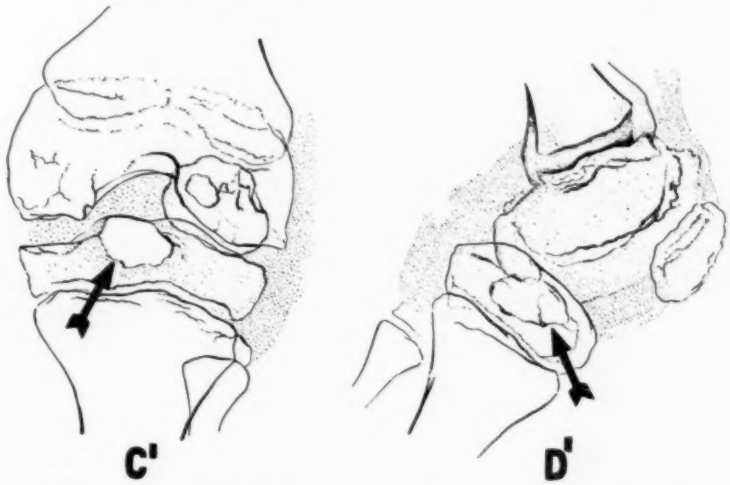

Fig. 1.—Cont'd. *C'* and *D'*, Semidiagrammatic representations of *C* and *D*.

Humeri		
Shafts		
Transverse axes	45	45
Anteroposterior axes	20	20
Capitellums		
Transverse axes	24	20
Anteroposterior axes	21	15
Vertical axes	15	12

The measurements show that all of the epiphyses are larger on the side of the hemarthrosis. It is noteworthy that the diaphyses of the right and left humerus have identical measurements despite the difference in the size and number of their epiphyses. This is not true of the radii, however, since the shaft of the left radius is larger than the right in both diameters although relatively it is not as disproportionate as are the corresponding epiphyses.

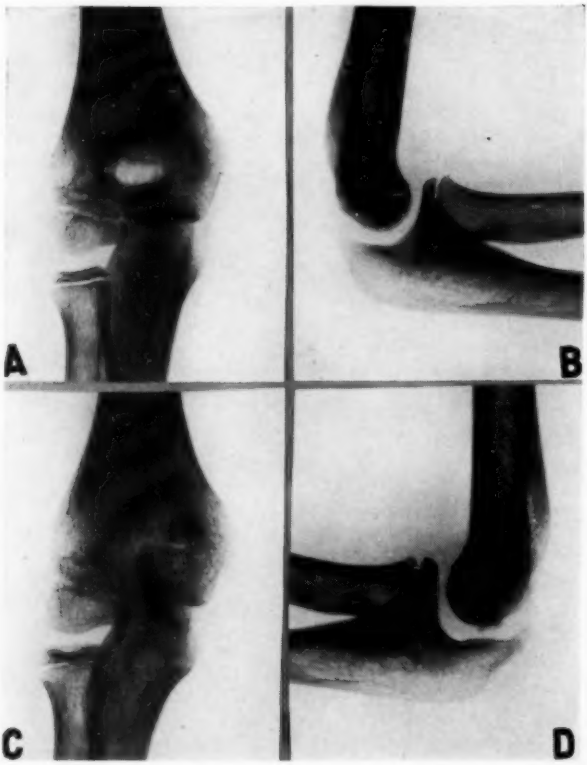

Fig. 2.—Case 1. Premature development of the epiphyses at the elbow with minimal deposition of iron in the soft tissues and without destructive changes in the bones (same patient as in Fig. 1).

A and *B*, Frontal and lateral projections of the normal right elbow.

C and *D*, Hemarthrotic left elbow. The accelerated development of the epiphyses is indicated by the increased size of all of the secondary ossification centers on this side and the presence of ossification centers in the trochlea and the olecranon.

CASE 2.—*Accelerated maturation and dysgenesis of the epiphyses at the elbow and intraosseous hemorrhage in the shaft of the radius.*

I. S. (B. H. 72721), male, was first examined for severe hemorrhage from the nose at 6 years of age. There were no known bleeders in the family. The patient had bled after mild trauma since early infancy. Circumcision was followed by profuse hemorrhage of two weeks' duration, and blue patches in the skin had come and gone almost continuously thereafter. Except for the epistaxis there were no significant physical findings. The clotting time was 24 minutes (capillary method), the bleeding time 8½ minutes, and there were 300,000 thrombocytes per cubic millimeter of blood. One week after the onset of epistaxis the left elbow became swollen and painful and remained so for several days.

The first bleeding into the right elbow occurred at the age of 6 years and 3 months, with simultaneous but smaller hemorrhages into the left elbow and the right ankle which disappeared after several days. In the right elbow the swelling

Fig. 3.—Case 2. Premature development of the ossification center of the epiphyses at the elbow with dysgenesis (flattening, cupping and irregularity in density) in the capitulum of the radius.

A and *B*, Frontal and lateral projections of the normal left elbow.

C and *D*, Frontal and lateral projections of the hemarthrotic right elbow. The secondary ossification centers are larger on this side. The ossification center in the olecranon is present and has already fused with the shaft (*D*) and the trochlear ossification center is clearly seen in *C*. The ossification centers in the olecranon and in the trochlea are absent in *A* and *B*. The capitulum of the radius is markedly enlarged, deformed, and irregularly mineralized. Opposite the arrow point in *C*, there is a sharply demarcated area of diminished density in the shaft of the radius, a "blood cyst" caused by intraosseous hemorrhage.

persisted, and two months later a second large hemorrhage occurred, causing limitation of motion for four months.

Roentgenograms of the elbows one year after the first hemorrhage into the right elbow are shown in Fig. 3. There are only slight increase in the periarticular soft tissue shadows, and mild, generalized osteoporosis of the bones on the right. Notwithstanding these almost negligible changes in the densities of the soft tissues and the bones, there are striking differences in the size and number of the epiphyses on the two sides. On the right, the secondary ossification centers in the olecranon of the ulna and the trochlea of the humerus are present and have already developed to a considerable size, while they are not yet visible on the left. The other secondary ossification centers are all larger in the right elbow than in the left. In the

capitulum of the right radius there is also dysgenesis of the enlarged center, as shown by the marked flattening of its vertical diameter and central cupping of the superior margin. In the proximal end of the diaphysis of the right radius there is an oval, cystic area of rarefaction which extends across the primary zone of calcification as far as the epiphyseal cartilage (opposite arrow point, *C*, Fig. 3). This lesion is similar to the cystic areas present in the epiphyses of the tibia and femur in Case 1. The measurements are as follows:

	Right	Left
Humeri		
Epiphyses		
Capitellums		
Transverse axes	24	18
Vertical axes	17	11
Trochleae		
Transverse axes	10	0
Vertical axes	8	0
Medial epicondyles—no significant differences		
Shafts		
Transverse axes	41	41
Anteroposterior axes	13	14
Ulnas		
Olecranons		
Transverse axes	9	0
Anteroposterior axes	4	0
Vertical axes	24	0
Shafts		
Transverse axes	20	18
Anteroposterior axes	28	27
Radii		
Capitulums		
Transverse axes	19	12
Anteroposterior axes	16	9
Vertical axes	4	2
Shafts		
Transverse axes	17	14
Anteroposterior axes	16	14

All of the secondary centers were significantly larger on the right, the side of the persistent hemarthrosis, excepting for the centers for the medial epicondyles, which had practically identical measurements. It is noteworthy that the ends of the diaphyses of the two humeri were equal in size while the ends of the shafts of the right radius and right ulna were significantly enlarged over the left; but relatively this difference in the size of the shafts is not so great as the differences in the sizes of the epiphyses.

This patient later had two hemorrhages into the left elbow and one hemorrhage into the right elbow. At 15 years roentgenograms of the elbows showed all of the secondary centers fused with their shafts with the exception of the medial epicondyles, which were equally developed. The right olecranon process was, however, larger than the left. The cystic lesion previously present in the right radius had disappeared.

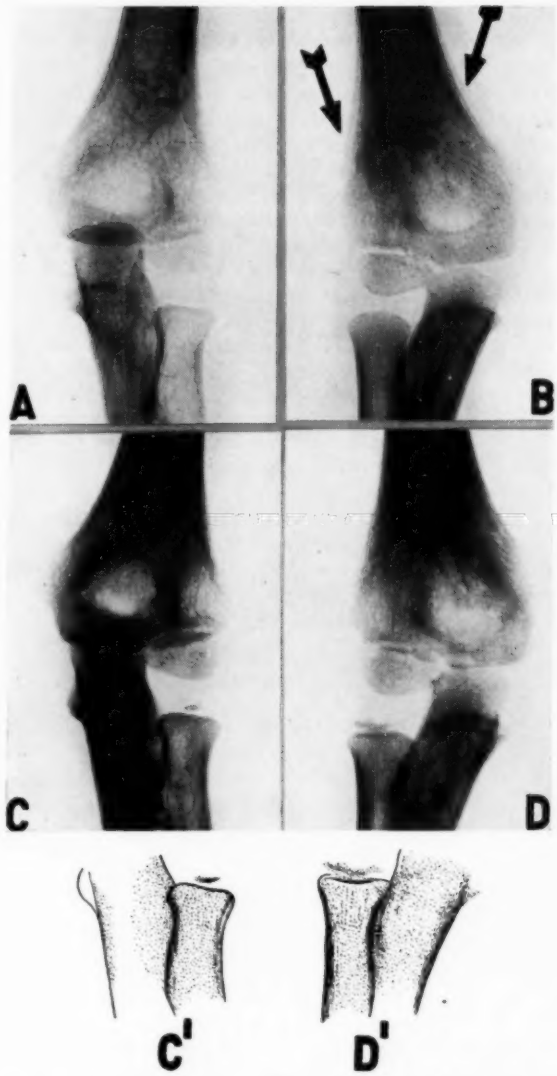

Fig. 4.—Case 3. Subperiosteal hemorrhage of the left humerus, overgrowth and fragmentation of the capitulum of the radius and hemarthrosis of the left elbow.

A and *B*, Frontal projections of the elbows one month after the initial bleeding into the left elbow.

A, Normal right elbow.

B, Hemarthrotic left elbow showing no changes in the epiphyses. The cortex of the humerus on both sides shows lamellated external thickening (opposite arrow points), probably the result of previous subperiosteal hemorrhage. There is a slight increase in the density of the soft tissues.

C and *D*, Frontal projections of the elbows seven months later than *A* and *B*.

C, Normal right elbow.

D, Hemarthrotic left elbow. Note the overgrowth of the capitulum of the radius with osteochondritic-like flattening and irregularity in density and outline. The thickening of the cortex of the humerus persists, but the lamellations have disappeared.

C' and *D'*. Semidiagrammatic representations of the capitulums in *C* and *D*.

CASE 3.—*Subperiosteal hemorrhage of the humerus, hypertrophy and fragmentation of the capitulum of the radius and hemarthrosis of the elbow.*

C. J. (B. H. 345157), male, had recurrent black and blue lumps in the skin during the first year of life. There had been known bleeders in three previous generations of his family. Profuse hemorrhage from the lips occurred at 1½ years of age. When the patient was first seen at 2½ years of age, he had numerous scattered ecchymoses. The coagulation time of the blood determined by the capillary method was 10 minutes, the bleeding time 2 minutes, and there were 760,000 blood platelets per cubic millimeter. At 4½ years of age severe bleeding followed biting the tongue during a paroxysm of whooping cough. Hemarthroses of both knees and of the left ankle developed in the fifth and sixth years.

At 7¾ years of age the patient fell on the left elbow, which became swollen, discolored, and painful. One month later flexion deformity and limitation of motion appeared. Roentgenograms made at this time (Fig. 4, *A* and *B*) show thickening and lamellation of the peripheral layers of the cortex of the left humerus and no evidence of a fracture line. Such cortical changes are frequently present in bones following subperiosteal hemorrhage. It is noteworthy that there are no significant differences in the development of the epiphyses on the two sides. There is a mild but distinct increase in the density of the soft tissues of the left elbow.

Roentgenographic examination of the elbow was made seven months later, Fig. 4, *C* and *D*, and the thickening of the cortex of the left humerus can still be seen. During the seven-month interval a striking enlargement of the capitulum of the left radius had taken place, and it was then more than three times as wide as the capitulum of the right radius (left, 10 millimeters, right 3 millimeters). In addition to this increase in the size of the left radial capitulum, its outline is markedly irregular and its density is uneven, resembling the changes of osteochondritis juvenilis.

CASE 4.—*Accelerated growth and maturation of the epiphyses at the knee with minimal changes in the diaphyses and soft tissues.*

W. P. (B. H. 318962), male, had bruised easily since early infancy. There were no known bleeders in the family. At 4 years of age he had a painful swelling of the right knee for about two weeks. At this time the coagulation time of the blood was 18 minutes, the bleeding time was 2 minutes, and there were 720,000 platelets in 1 c.mm. of blood. During the ensuing two years he had several recurrent swellings of the right knee which, however, did not leave residual disability.

Roentgenograms of the knees taken two years after the initial right hemarthrosis are shown in Fig. 5. The periarticular soft tissues show some increase in density, and the articular surfaces of the condyles of the right femur have an irregular margin, particularly the medial condyle. The density of the bones, however, is approximately equal on the two sides, and there is little, if any, destruction of bone and cartilage similar to that present in the knee in Case 1. Notwithstanding the absence of destructive changes, the epiphyses of the right femur and of the right tibia are significantly increased in size, as shown by the following measurements.

Femurs	Right	Left
Epiphyses		
Transverse axes	55	55
Anteroposterior axes	40	33
Vertical axes	22	18
Shafts		
Transverse axes	54	54
Anteroposterior axes	33	30

Tibias		
Epiphyses		
Transverse axes	46	42
Anteroposterior axes	32	28
Vertical axes	16	15
Shafts		
Transverse axes	46	42
Anteroposterior axes	30	32
Patellas		
Anteroposterior axes	10	5
Vertical axes	18	15

This case demonstrates that the accelerated growth of the epiphyses in hemophilic hemarthrosis of the knee is not necessarily associated with severe destructive changes in the bone and cartilage.

Fig. 5.—Case 4. Minimal changes in the bones and soft tissues with accelerated growth and development of the epiphyses at the knee.

A, Lateral projection of the normal left knee.

B, Lateral projection of the hemarthrotic right knee. The epiphyses and patella are larger on this side, but there is no generalized demineralization or focal destruction of the bones as in Fig. 1, *C* and *D*. The articular surface of the medial condyle of the femur is irregular.

CASE 5.—*Hemarthrosis of the hip joint with coxa plana resembling Perthes' disease.*

J. B. (B. H. 474892), 10 years of age, had been a bleeder since he was 2 years old. Hemorrhagic diathesis had not been recognized in other members of his family. At 8½ years of age hemorrhage occurred into the right hip joint, which became swollen and tender. He was admitted to the hospital at 10 years of age because of a limp in the right leg. Forced motion of the hip joint was painful, and there was marked limitation in motion. The coagulation time was 19 minutes (capillary method), the bleeding time 1½ minutes, and there were 450,000 blood platelets per cubic millimeter.

Roentgenograms of the hips (Fig. 6) show a diffuse osteoporosis of the bones contiguous to the right hip joint. On the superior margin of the proximal epiphysis of the right femur there are two large areas of destruction, and there is a flattening

and horizontal spreading of the epiphysis without reduction in the depth of the joint space. The neck of the right femur is widened, but there are no focal areas of destruction in the diaphysis. Projecting caudad and laterad from the lateral end of the roof of the acetabulum there is a heavy spur 11 millimeters in length and a smaller spine projects downward and inward from the medial end of the roof of the acetabulum. A slight increase in density is present in the soft tissues of the joint. Measurements were as follows:

Femurs	Right	Left
Epiphyses		
Transverse axes	49	44
Vertical axes	10	17
Shafts		
Transverse axes (at cartilage-shaft junction)	46	42
Transverse axes (narrowest diameter of neck	35	30

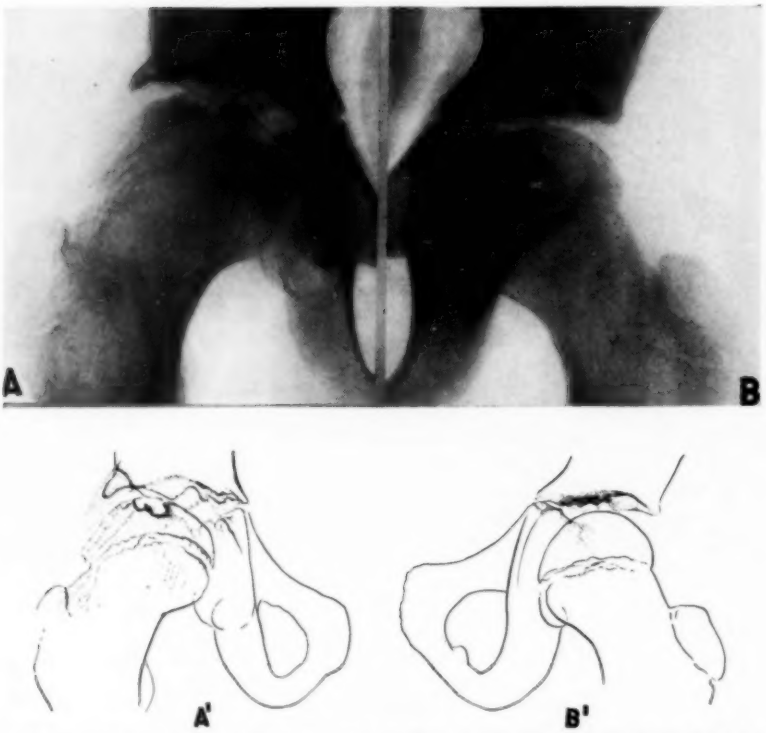

Fig. 6.—Case 5. Hemarthrosis of the right hip with coxa plana resembling Perthes' disease and large marginal defects in the epiphyses caused by subchondral hemorrhage.

A, Frontal projection of the hemarthrotic right hip. There is a diffuse osteoporosis of the femur. The epiphysis is flattened and has several large defects in the region of the fovea capitis femoris. The joint space, however, is well preserved. Bony spines project from both the lateral and medial margins of the roof of the acetabulum.

B, Frontal projection of the normal left hip.

A' and *B'*, Semidiagrammatic representations of *A* and *B*.

The measurements of the shaft show that the shaft of the femur participated to a greater degree in the enlargement than was the case with the shafts of the bones contiguous to the hemarthroses in the knees and elbows.

COMMENT

There is a considerable difference of opinion concerning the frequency of articular involvement in hemophilia. Some writers have claimed that bleeding into the joints occurs in all hemophiliacs, while others have found that less than one-third of their hemophilic patients had hemarthroses.[8] In the large group of ninety-eight hemophiliacs studied by Thomas[3] 78 per cent gave a history of joint involvement, and 61 per cent had permanent deformities. In this same group the distribution of the arthroses was as follows: knees, 68 per cent; ankles, 56 per cent; elbows, 53 per cent; hips, 16 per cent; fingers, 15 per cent; and toes, 2 per cent. In all reports the knees are most frequently affected, probably because of their relative easy vulnerability to injury and the difficulty of protecting them in walking.

The present knowledge of the morbid anatomy of the hemophilic arthropathies is based on König's original descriptions[16] in 1892, which were later confirmed and amplified by Freund[17] and by Reinecke and Wohlwill.[18] Key[2] made detailed microscopic studies of the synovia and the subsynovial tissues in 1932. Nearly all later writers have accepted König's findings and have adopted his division of hemophilic hemarthrosis into the three sequential stages; acute simple hemarthrosis, panarthritis, and the stage of regression. The following summary of the clinical, anatomical, and roentgenographic findings in these three stages have been taken from the reports of the authors mentioned above and the later writings of Klason,[8] Firor and Woodhull,[19] and Prip Buus.[20]

Simple Hemarthrosis.—The onset may occur spontaneously or after minor injury, and the clinical picture is determined by the amount and the rapidity of the bleeding. Characteristically the articular swelling develops rapidly in a few minutes or hours. When the intra-articular hemorrhage is large, there is extreme distention of the joint, and all motion and even weight-bearing may be prevented by the severe pain. Examination of such a patient discloses the markedly swollen and tender joint with limitation of motion. There may or may not be an increase in the local heat, and at the large joints there is usually no discoloration of the skin. The constitutional symptoms are usually limited to fever, which may reach 104° F. in severe cases. Moderate leucocytosis frequently accompanies the fever. When the intra-articular bleedings are smaller in volume, the local findings are less

marked, and there may be no constitutional symptoms. In many instances blood is completely absorbed from the joint within a few weeks, and there is a synchronous progressive return of function. Klason[8] cites Gocht's interesting patient who had forty-five hemorrhages into one joint with only slight permanent disability.

The only anatomic finding in this early stage of hemarthrosis is the hemorrhage in the joint space. Roentgenograms show mild diffuse increase in density of the soft tissues with or without distention of the joint space. Case 3, Fig. 4, *A* and *B*, with examination one month after the first hemorrhage into the elbow, is a good example of acute hemarthrosis. In this instance there is also a subperiosteal hemorrhage of the humerus.

Panarthritis.—The absorption of intra-articular blood may be incomplete after the initial hemorrhage or after recurrent hemorrhages, and the retained blood and blood clots produce a chronic inflammation of the synovial membrane. In such cases the joint remains swollen, tender, and painful for several months or years with variable degrees of disability. After each recurrence of bleeding, the picture of acute hemarthrosis is repeated, followed by partial subsidence of the symptoms in the intervals between acute exacerbations. Gradually, however, the chronic irritation produces a permanently swollen joint with local deformity, contractures, muscle atrophy, and a cumulative loss of motion. The articular capsule becomes thickened and even sclerosed, and in some cases crepitation may be present. Key[2] points out that the articular swellings tend to be smaller in this second stage than in the stage of simple hemarthrosis because the heavy subsynovial fibrous tissue in panarthritis prevents extreme distention of the joint spaces.

There is a variety of pathologic changes caused by chronic irritation of the synovia, by the hemorrhages into the joint space and into the bones, and by the disuse of the part. The synovial membrane hypertrophies with the formation of folds and villi and a dense layer of subsynovial fibrous tissue. The soft tissues in and around the joint become saturated with iron-containing blood pigments. Freund[17] found that 71 per cent of the ash of the synovial membrane was iron. In Key's reproductions of roentgenograms of pieces of the synovial membrane, there are shadows of heavy mineral density which he attributed to the high iron content of the synovial tissue.

The articular cartilage may be eroded at the margins of the joint from the encroachment of the thickened synovial membrane, and in addition there is an irregular maplike destruction of cartilage in the central portions which Key[2] believed to be characteristic of the hemophilic joint. The portions of the bones contiguous to these latter areas of cartilaginous destruction are invaded by connective tissue,

producing irregular erosions of the articular surfaces of the bones themselves. Larger, punched-out areas of destruction are sometimes produced on the articular margins of the bones by subchondral hemorrhage; and deeper in the cancellous structure, completely separated from the borders of the bones, cavitation may be caused by intraosseous hemorrhage. Reinecke and Wohlwill[18] have demonstrated extensive destructive and productive changes in the cortices of the shafts in association with subperiosteal hemorrhages. In addition, there is a diffuse demineralization of the involved bones secondary to the atrophy of disuse.

There are marked roentgenographic findings, as might be expected from the extensive anatomical changes. The shadows of the soft tissues show an increased density which at times approaches calcium density because of the high iron content of the synovial and subsynovial tissues. The joint space may be reduced because of the deficiency of articular cartilage. The articular surfaces of the bones are irregular because of the more central focal subchondral bone destruction, and there may be large oval cystic defects in the margins of the bones secondary to subchondral hemorrhage. Completely separated from the articular margins, sharply outlined oval areas of rarefaction may be present, which result from intraosseous hemorrhage, and the ring shadows limiting these cavities are said to be caused by compression of the cancellous structure by the expanding hematoma. Several of the roentgen features of severe long-standing panarthritis are seen in Fig. 1, Case 1. The large marginal erosions of bone secondary to subchondral hemorrhage are well demonstrated in Fig. 6, Case 5, on the articular border of the femoral epiphysis. The minimal changes in early panarthritis are seen in Fig. 5, Case 4.

The Stage of Regression.—This terminal stage of the lesion is not sharply differentiated from the panarthritic stage. There is a tendency toward healing with the clinical picture of pseudoarthritis deformans resulting in either fibrous or bony ankylosis. We have not examined patients in this stage.

Firor and Woodhull[19] have pointed out that in the smaller articulations the regressive stage does not develop because the weaker joint structures and the thinner cortices of the smaller bones cannot hold the progressively expanding hematomas in check. In a case described by them there was complete destruction of the joints and bones of a metacarpophalangeal articulation with rupture of the soft tissues and skin. The preoperative roentgen diagnosis was sarcoma because of the extensive bone destruction.

It is surprising that subperiosteal hemorrhages do not occur more frequently in hemophilia. We encountered roentgen evidence of sub-

periosteal hemorrhage in one of the eleven hemophiliacs studied, Fig. 4, Case 3. Although subperiosteal hemorrhage is mentioned by several writers as a skeletal complication of hemophilia, one gets the impression that it is relatively infrequent. Reinecke and Wohlwill[18] have described an extensive subperiosteal hematoma of the femur in one case associated with intra-articular hemorrhage in the knee, and in a second case subperiosteal hemorrhage in the proximal end of the ulna was associated with hemarthrosis of the elbow.

We were unable to measure the effect of chronic hemarthrosis on the growth of the diaphyses because the entire shafts of bones contiguous to the hemophilic joints were not included in our roentgenograms. Harris[21] has reported overgrowth of 1 inch in the left lower extremity, one and one-half years after bleeding into the left knee, in a hemophiliac 11 years of age. It is not clear whether this increase in the total length of the extremity was caused by overgrowth of the shaft or by overgrowth of the epiphyses, since only external measurements of the leg are reported. It is surprising that excessive growth in length of the shaft has not been reported in hemophilic hemarthrosis because bleeding into the joint induces a chronic irritation and chronic hyperemia. Longitudinal overgrowths of the shafts have been reported in many conditions which have chronic hyperemia, both active and passive, as a common factor; namely, arteriovenous aneurysms, hemangiomas, lymphangiomas, patients with prolonged cellulitis, chronic inflammations of the bones and joints, and healing fractures. It is highly probable that the acceleration of development and overgrowth of the epiphyses observed in our group of cases was caused by excessive flow of blood to the growing epiphyses over periods of several months or years.

Artificial chronic hemarthroses did not accelerate the development of the epiphyses in growing rabbits observed by us. Heparinized blood was injected into the knee joints of rabbits, beginning in the second week of life. The injection was repeated three times each week until the rabbits were 8 weeks old. Serial roentgenograms showed that epiphyseal development was not advanced in the experimental animals in comparison with uninjected litter mates. Necropsies on several of the animals demonstrated that the blood had been injected into the joint cavities and not into the periarticular tissues.

The development of coxa plana resembling Perthes' disease in hemophilia emphasizes the multiple causes of this deformity and demonstrates that Perthes' disease is a symptom complex rather than a disease entity in itself. We have now seen Perthes' deformity in thyroid deficiency, congenital dislocation of the hip, chondrodystrophy, hemophilia, and in the irregular, generalized dyschondroplasias such as Morquio's disease and Hurler's syndrome (gargoylism).

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A NEW TREATMENT FOR FURUNCULOSIS (SULFAMETHYLTHIAZOL)

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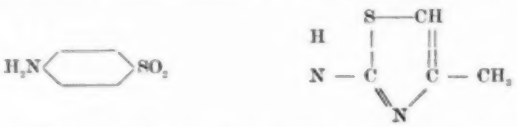
ONE of the most baffling conditions which the physician has to meet in infants is furunculosis. One is impressed, in going over the literature, with the number of different treatments which have been advised; this, as usual, means that no one of them is satisfactory.

It is well known that furunculosis is characterized by a marked tendency to extend locally, especially in the scalp, to resist all forms of treatment, and to await the development on the part of the child of an immunity before the condition clears up. Any treatment which offers a possible solution to these difficulties is, therefore, a boon to the physician and the patient.

There has recently been developed a drug, sulfamethylthiazol,



which is reputed to have a very beneficial effect on animals in staphylococcus infections. It was thought, therefore, that it might be advisable to try this drug in the treatment of furunculosis in infants.

CASE 1.—C. W., a 2½-month-old female infant, was sent to the Presbyterian Hospital on April 21, 1939, because of a swelling which had been present on the back of her head for about a week. This tumor mass had gradually increased in size until, at the time of admission, it was about as large as a hen's egg. For two days prior to admission, the child had been fretful and, the mother thought, feverish.

Past history was negative. There had been no significant trauma to the head at birth. The baby was breast-fed. She was pale, but in a good state of nutrition.

Examination at the time of admission revealed a fluctuant mass over the right occipital region of the scalp. The temperature was 102° F.

Examination of the blood showed hemoglobin, 55 per cent (Dare); red blood count 2,750; white blood count, 15,800, with polymorphonuclears, 70 per cent, small mononuclears, 25 per cent, and large mononuclears, 5 per cent. Examination of the urine was negative. Roentgenograms of the skull showed no bony abnormalities.

The child was given 150 c.c. of citrated blood by indirect transfusion.

The tumor mass was surgically drained of about 10 c.c. of thick, bloody material in which many "flakes" of greenish pus were seen. Culture of this material yielded a hemolytic streptococcus.

Accordingly, sulfanilamide in adequate dosage was prescribed. Within three days, however, numerous new pustules had appeared throughout the child's scalp and on her

From the Pediatric Wards of the Presbyterian Hospital, Chicago.

neck, back, and abdomen. Blood culture was negative, but culture of these new pustules yielded a hemolytic staphylococcus. The sulfanilamide was discontinued.

Two weeks after admission, during which time small furuncles were daily incised, a particularly large and diffuse swelling appeared on the right parietal region of the scalp. This mass was drained under anesthesia by a member of the surgical staff who described the abscess cavity as being subaponeurotic in its location. The periosteum of the skull was laid bare by the incision necessary to reach the pus.

Seemingly, it was from this abscess that the infection burrowed beneath the scalp to persist for the following nine months. During this time new furuncles "pointed" almost daily and made drainage necessary. We estimate that about 450 individual abscesses were drained during this period.

A variety of local antiseptics, in addition to general measures, were employed during this time. The head was kept shaved. Alcohol packs, bichloride of mercury dressings, potassium permanganate, gentian violet, silver nitrate, tincture of iodine, ultraviolet irradiations, and x-ray therapy were employed without appreciable effect. In conjunction with the local therapy, the following general measures were given adequate opportunity to demonstrate their ineffectiveness:

1. Sulfanilamide, as mentioned above. No beneficial effect.

2. Autogenous vaccine. During the administration of the vaccine the infection seemed to get worse.

3. Oxide of tin (stannoxyl). Given in the recommended doses for a period of four weeks without benefit.

4. Staphylococcus toxoid (Lederle). The prescribed course was given to no avail.

5. Sulfapyridine. Twice attempted, but provoked vomiting after about three days both times; no effect noted.

6. Blood transfusions were frequently given. In all, 1,200 c.c. of blood was given the child during the period of her hospitalization.

It was interesting to observe that during this long period, and despite her infection, the child gained and developed in a normal fashion. Except during periods of intercurrent respiratory infection and occasionally during the development of particularly large abscesses, she was afebrile. Her weight, which was 11 pounds 9 ounces (5,460 Gm.), is now (Jan. 26, 1940) 20 pounds 2 ounces (9,660 Gm.).

On Dec. 22, 1939, eight months after admission to the hospital, treatment with sulfamethylthiazol was begun. One-half gram of the drug was administered every four hours. This dosage produced no symptoms and effected a level of about 8 mg. per cent in the blood.

Improvement in the child's condition was apparent after about forty-eight hours. During this time, old (draining) furuncles dried up almost completely, and for several days, no new pustules were observed. The drug was given in this dosage for twenty-two days, or until 66 gm. had been administered. During this time only five new furuncles appeared, and when a week had passed without further evidence of activity, the drug was stopped. There had been no ill effects noted during this rather long period of therapy. Blood and urine examinations revealed no significant changes. There was no nausea or vomiting.

On Jan. 1, 1940, three small abscesses were opened, and the cultures were positive for *Staphylococcus hemolyticus*.

Two days after discontinuing the drug, however, two new abscesses developed on the scalp. Fearing a relapse, sulfamethylthiazol was again employed. This time, after eight doses (4 Gm.), a sudden reduction from 31 to 10 in the percentage of polymorphonuclear cells occurred, and the drug was stopped. The scalp was again "dry," however, and no new furuncles have appeared since then (Jan. 25, 1940). The blood picture slowly returned to normal.

All who observed this miserable child during her long hospitalization were much impressed by the change in her appearance after therapy with the drug had begun.

CASE 2.—R. A., a 7-month-old male infant, was seen in the Central Free Dispensary, with the complaint of boils on the scalp of several days' duration. For about four days (preceding admission to the hospital) the child had had coryza. Because of our desire to observe the effect of sulfamethylthiazol in another case of furunculosis, he was admitted to the hospital for therapy.

Examination at the time of admission revealed a small, fairly well-nourished, Mexican infant on whose scalp were seen twelve furuncles in various stages of evolution, from small papules to frank pustules. In the region of the right temple was a diffuse subcutaneous abscess surrounded by an area of edema which extended to involve the eyelids, almost closing the eye on that side. There was a mucopurulent nasal discharge and a profuse postnasal drip. The temperature was 101° F.

Laboratory studies showed a negative urine; hemoglobin of 70 per cent (Tallqvist); red blood count, 4,800,000; white blood count, 24,000, with polymorphonuclears, 41 per cent, small mononuclears, 51 per cent and large mononuclears, 8 per cent.

One furuncle was drained for purposes of culture. A hemolytic staphylococcus was found.

Sulfamethylthiazol in a dose of 0.5 Gm. every four hours was given. There was no other therapy. Within twenty-four hours the improvement in the child's appearance was striking. The edema surrounding the abscess on the right temple had completely disappeared, and the abscess itself was almost entirely dried up. The temperature was normal. Improvement in the other furuncles was quite apparent and continued throughout the following days of therapy until all evidence of active infection had disappeared.

Treatment according to the dosage mentioned above was maintained for three and two-thirds days, after which the child had received a total of 11 gm. of the drug. By this time, the infection was almost completely healed, but it was deemed advisable to continue administration of the medicine in smaller doses as a precaution against reinfection. Accordingly, 0.064 Gm. was given every four hours during the remaining nine days of the child's hospital stay. A total of 14.5 Gm. of sulfamethylthiazol was given him without untoward effect. There was no vomiting. On the day of discharge the child's blood studies showed hemoglobin to be 75 per cent and the white blood count, 15,000, with a normal distribution of white cells. The blood level was 5.2 mg. on Jan. 13, 1940 (small dose). When the child left the hospital on the twenty-third day, the scalp was entirely free of pustules.

CASE 3.—Opportunity to test the efficacy of sulfamethylthiazol in a third case of furunculosis appeared when A. P., a 7-year-old boy (on the cardiac service of the Presbyterian Hospital Pediatric Wards), developed several pustules in his scalp.

One gram of the drug was given every four hours. Improvement, though less striking than in the other cases, was apparent. Six days after the beginning of therapy, the scalp lesions were almost completely healed. A total of 37 Gm. was used.

On the third day of drug therapy, the child was nauseated and vomited twice after medication had been given. He complained of abdominal pain and anorexia. On the seventh day a generalized morbilliform rash appeared on the body. There was no other evidence of a contagious exanthema, and the eruption was considered a toxic manifestation of the drug. Further medication was discontinued, and within twenty-four hours the rash had completely disappeared.

There was no change effected in the child's blood or urine during the medication. Blood levels of the drug were not estimated.

SUMMARY

These three cases show the effects of sulfamethylthiazol in the treatment of furunculosis in infants. However, the drug must not be used unless there is careful observation.

In one case, there was a toxic rash which could scarcely be ascribed to anything but the drug. The vomiting in that case may or may not have been due to the drug, since the boy had been in the ward a long time and had frequently had periods of vomiting. Of a much more serious nature is the neutropenia which developed in the first case. However, this developed only after prolonged use. That the drug had the effect it did in the first case is very encouraging, because this case was the most severe case of furunculosis that any of us had seen. It should be noted, however, that on the tenth day after medication was started in this case, the abscesses still showed positive cultures.

CONCLUSIONS

Sulfamethylthiazol had a beneficial effect in three cases of furunculosis in infants and children. Untoward symptoms developed, consisting of vomiting, toxic rash and neutropenia. All of these cleared up without any serious aftereffects.

Drug was furnished by the Department of Medical Research, Winthrop Chemical Co., Inc.

NOTE: The following development of Case 1 may be of interest. From January 29 until February 28, the child did beautifully; in fact, she was ordered discharged on February 28. Before this could be accomplished, the child's temperature rose to 100.8° F., and by February 29, it had reached 103°. This was accompanied by coryza and a definite pharyngitis which continued. Vomiting took place and the temperature rose rapidly to 105° on March 1. The child died at 5:15 P.M., one hour after generalized convulsions. Unfortunately, no autopsy was obtained.

It is interesting to note that sulfanilamide was started on February 29, but had no effect whatever on the course of the disease, which apparently, from the cultures, was a streptococcus sore throat. It should be noted, however, that there was a tendency for this child to have low polymorphonuclear counts after the sulfamethylthiazol had been given for some time. The polynuclear count was as follows: January 31, 29 per cent; February 8, 12 per cent; February 15, 17 per cent; and February 23, at which time the drug was discontinued, 3 per cent. Just before death, the white blood cell count was 20,000, with polymorphonuclear cells, only 5 per cent.

THE BEHAVIOR EXAMINATION OF INFANTS AS AN AID TO EARLY DIAGNOSIS OF CENTRAL NERVOUS SYSTEM DISEASE

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IT IS becoming more and more evident that the psychologic examination is an important adjunct to many aspects of pediatric practice. In cases of cretinism it is the behavior change in excess of that occurring normally with advancing age which demonstrates the effectiveness of thyroid therapy.[3] It is the psychologic examination that helps determine whether maladjustment is due to slow mental growth or to a nurse-child or parent-child relationship.[4] It is the behavior examination which aids in the evaluation of the potentialities of infants injured at birth or those with other types of motor handicaps.[6] The degree of pervasiveness of such defects as blindness or deafness can be adequately appraised only by careful psychologic study which evaluates the child's behavior response in terms of his handicap.[9] Eye-hand incoordination, not evident to the oculist or neurologist, is revealed by psychometric analysis.[4] Furthermore, it is the behavior examination which helps attain an understanding of the child's problems of adjustment or mental hygiene requirements, just as the physical examination is essential to a diagnosis of bodily illness.[10]

Recently another contribution of the psychologic examination to pediatric practice has been demonstrated. Two infants were referred for psychologic study because of feeding difficulty. In both instances study indicated central nervous system abnormality not suggested by either the pediatric or the neurologic examination. The abnormality was confirmed by encephalography and by the subsequent development of the children.

CASE REPORTS

CASE 1.—N. J., a male infant, was the result of the first pregnancy of a 25-year-old unmarried mother. She was a high school graduate who manifested definite psychoneurotic tendencies; the father was a professional man. Medical (ergot) and instrumental attempts at abortion during early pregnancy failed. Delivery was at term by low forceps, without apparent injury.

The child was institutionalized at the age of 12 weeks. Physical examination at that time was essentially negative. The routine psychologic examination* at 16 weeks was likewise unremarkable, except for slight hypertonicity (fisted hands and head retraction) and unusual attention for the examiner rather than for test objects. Incipient reaching for the dangling ring, an adequate response for this age, was elicited. The child appeared normal to the nursing personnel of the institution until

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*Methods and norms are those established by the Yale Clinic of Child Development.[2, 8]

the age of 4 months when solids were introduced into his diet; then feeding became difficult. He also appeared disinterested in toys. At 6 months of age thumb-sucking and head rolling were prominent. Psychologic examination at 28 weeks of age revealed atypical behavior (Fig. 1) which is summarized as follows:

Postural behavior was unusually variable. When the child was pulled to a sitting position, the head sometimes lagged seriously, while at other times it was held normally in line with the body. Placed sitting, the child occasionally sat momentarily erect, as we expect at this age, but usually he leaned completely forward. Posturally, he appeared relaxed and disinterested, rather than merely retarded.

In contrast to the relaxed body posture, the hands were held fisted (12 weeks).* When the child was supine, reaching was a variable response; but when he was supported sitting, the response could not be elicited (20 weeks). Instead of reaching, the child held his hands fisted and drawn back while the head was brought forward

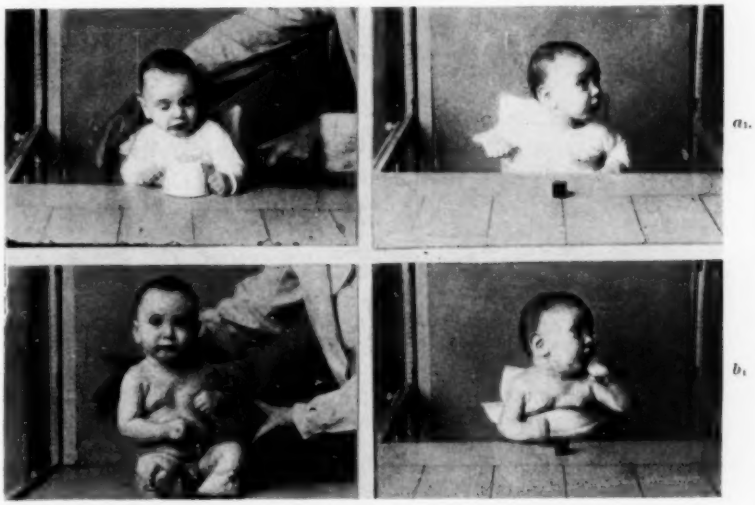

Fig. 1.—Case 1, N. J. *a*, Age 28 weeks. Showing fisted hand (unusual after 12 weeks), and preferential attention for examiner (uncommon behavior); *b*, Age 36 weeks. Showing sitting posture (normal), and preferential attention for examiner. Note fisted hands.

as he stared at the objects. The small pellet was regarded only momentarily without overt response (20 weeks), as contrasted with the normal 28-week behavior of consistent regard and attempt at prehension. The child spent long periods in hand and foot play (24 weeks), and at times objects moved even in his line of vision failed to elicit regard (less than 16 weeks). Emotionally and socially, N. J. appeared normally responsive.

The above behavior is decidedly asymmetrical and atypical. It is normal with respect to the maximal postural and supine prehensory responses. It is abnormal with respect to hand posture and eye-hand coordination in sitting, and especially in the variability of the maximal responses in all test situations. Diagnostic possibilities were: (1) cerebral defect, (2) birth injury, (3) degenerative disease, and (4) institutional conditioning. Behavior was too irregular to suggest ordinary mental deficiency. Institutional conditioning might explain the unresponsiveness to

*Ages in parentheses refer to the normative age.

toys in contrast to the vivid social response, but it did not account for the atypical hand posture. Cerebral defect or degenerative disease seemed the most likely diagnosis.

The neurologic examination one week later reported merely that the child appeared dull and fixed attention only momentarily. Play periods to offset any possible institutional conditioning were planned, and foster home placement was finally made.

Periodic re-examinations showed progressive retardation and continued flashes of normal behavior, interspersed with periods of remarkable unresponsiveness. Thumb-sucking, head rolling, rocking back and forth when sitting, rolling of the eyes, and unusually long periods of crying became common.

Encephalography was finally undertaken at 13 months of age. The spinal fluid showed normal sugar, protein, and cell content. A large amount of subarachnoid air was present over both cerebral hemispheres, with a symmetrical increase in the size of the subarachnoid spaces, most marked in the frontal and parietal areas. Patchy residual collections of subarachnoid air were present in the films taken twenty-four hours later. The roentgenologic diagnosis was cortical atrophy.* (Fig. 2.)

These findings corroborated the early impression of brain defect. The child's subsequent development likewise confirmed this impression. Briefly his progress has been as follows.

The motor development has been near normal. At 18 months of age, he walked when only one hand was held to supply balance (15 months); at 2 years he was able to walk proficiently, squatting and rising in his play (21 months); at 3 years he walked upstairs with alternate feet (36 months); and at 3½ years he walked downstairs, one foot at a time (48 months); but he could not stand on one foot (42 months). Balance was always poor; he moved slowly and cautiously.

Eye-hand coordination developed slowly. Even at the age of 18 months he tended to drop what he was holding in one hand as he reached and grasped with the other (28 weeks). He did, however, release one cube over another (1 year). When he was 2 years old, he built a tower of two blocks (15 months); at the age of 3 years he piled six blocks (2 years), and at 3½ years he once piled ten blocks (3 years). His performance was highly variable.

Language has been acquired slowly. At 18 months he responded to "no-no," "sit down," and "come" (1 year). At 2 years he said "ta-ta" and conversed jargonwise (15 to 18 months). At 3 years he said single words (18 months). At 4 years and 9 months he used sentences spasmodically. Frequently he replied with a stereotyped and meaningless "no."

Habit training has been slow and difficult. However, he learned to feed himself at the age of 3½ years, and by 4½ years he was reported to ask for the toilet during the day (21 months).

Between the ages of 15 months and 2 years many behavior deviations, such as making "hideous noises," shaking his head hard and fast, sputum play, teeth grinding, hysteria, and temper tantrums, appeared. Foster home replacement was made with subsequent improvement. Stereotyped behaviors, such as turning round and round, placing books upright in windows, and swinging the door back and forth for long periods, continued to develop and disappear in accord with his behavior growth. The foster mother continued to report that he seemed out of contact with his environment and heeded her only after many repetitions. But it is of interest that by the age of 3½ years he had learned to put dishes on the table in their correct places. Despite his atypical traits, visitors in the home have never considered him a retarded child.

*The authors gratefully acknowledge the assistance of Dr. Hugh M. Wilson of the Department of Radiology in the interpretation of the roentgenologic findings.

Fig. 2.—Case 1, N. J. Posteroanterior and lateral encephalograms made with child erect, demonstrating widened sulci, poor filling of lateral ventricles, and subdural collections of air.

His behavior deviations could be misinterpreted easily as emotionally conditioned. The improved behavior following replacement suggests that certain behavior may have been due to improper handling. There is little doubt, however, that the indifferent, self-directed, stereotyped behavior apparent from early infancy has an organic basis.

CASE 2.—D. C. was the child of a 20-year-old unmarried domestic servant. The father's identity was questionable. As far as is known, pregnancy was uneventful. Delivery by low forceps, at term, resulted in a cephalohematoma of the left parietal region which subsequently calcified and resorbed within the first year of life. Other than this, the physical examination at birth was negative.

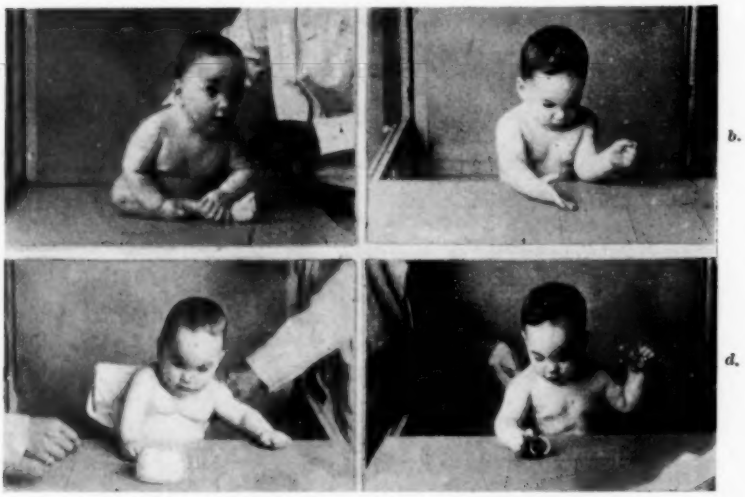

Fig. 3.—Case 2, D. C. *a*, Age 29 weeks. Sitting posture normal; *b*, Age 1 year. Unsuccessful pellet prehension (less than 32 weeks), with hand supinated rather than pronated as usual; *c*, Age 29 weeks. Child regarding cup with extended arms (28 weeks), and fisted hands (12 weeks); *d*, Age 1 year. Child grasping objects with unusually hyperflexed digits of right hand.

The child was institutionalized at the age of 24 weeks. The only abnormal finding of the admission physical examination was a markedly dolichocephalic head with a bony ridge along the line of the frontal suture. D. C. was referred for psychologic examination because of feeding difficulty. He would either passively hold solids in his mouth, refusing to swallow, or regurgitate by thrusting his fist in his mouth.

Psychologically, D. C. presented an irregular atypical behavior pattern similar to our first case. The examination at 25 weeks revealed that posturally the child's behavior was, in general, at the 24 weeks level (Fig. 3); he sat leaning forward and supported his weight when held standing. His prehensory behavior was retarded about four weeks; he reached for no objects until they were within a few inches of his hand. Retention of objects placed in the hand was very brief. As soon as the object in the hand had been regarded, it was dropped, and the hand was regarded. Perceptually his behavior was at the 12 to 16 weeks level; he regarded a cube only briefly, and stared at the cup with head strained forward. The most mature aspect of the child's rattle play was transferring it from one hand to the other, a response normal for this age, but this behavior was variable. Usually the child dropped the rattle and regarded his own hand (12 weeks).

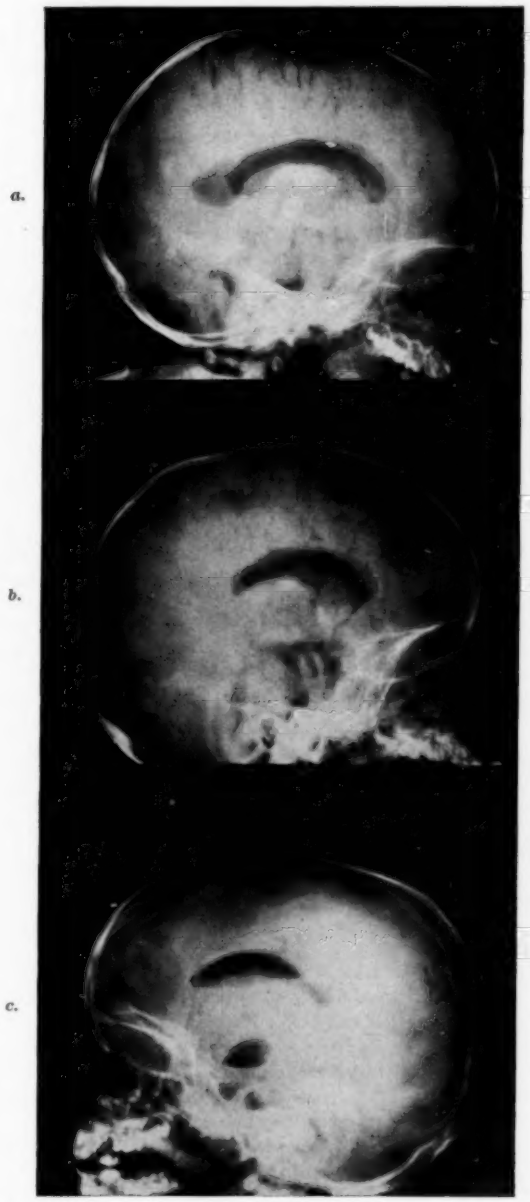

Fig. 4.—Case 2, D. C. *a*, Lateral encephalogram with child erect, demonstrating dilatation of ventricular system and deformity of basal cisterns; *b*, Lateral view with air in frontal horns, demonstrating suprasellar air pocket and abnormal subarachnoid sulci; *c*, Twenty-four-hour lateral view demonstrating residual air in porencephalic cyst.

Thus, the abnormality with respect to prehension and perception suggested mental retardation, but the etiology of this scattered performance was quite as puzzling as that in Case 1. Foster home placement was made, and the psychologic study was continued.

Neurologic examination at the age of 7 months was completely negative, and several competent medical observers felt that the child was not mentally defective. Accordingly, encephalography was postponed a year, during which time repeated observation and psychologic examination confirmed our initial observations. For example, when he was 1 year old, he walked when one hand was held (1 year). Although voluntary release of the cube in the cup was promptly elicited, D. C. was unable to pick up the small pellet, a skill common at 32 weeks and normally invariably present at 40 weeks (Fig. 3). Grasp was unusual; the thumb did not oppose the fingers on the cube (an immature response), and frequently the hand was held supinated in attempting prehension (an abnormal attitude). Perceptive behavior was more mature, but not up to age; he showed that he noticed the pellet in the bottle by poking at it, but he disregarded the pellet when it dropped from the bottle, behavior uncommon after 40 weeks. Cooperative ball throwing (1 year) was elicited at favorable moments; at times he was socially responsive, but at other times he was inattentive.

At the age of 15 months he was walking alone, but he had not yet attained the manual skill characteristic of an 11-month-old child. Examination at 16 months revealed that, except in gross posture, there were no behavior responses in advance of the 1-year level. Developmental progress in the preceding six months had been slight. His attention for the test toys was brief, and behavior was difficult to elicit. His face was nonexpressive, and it was impossible to obtain ocular pursuit of objects for an arc of more than 10°. In response to a moving object, he shifted his regard or turned his head without moving his eyes. He gave the impression of having a cerebral defect of a fairly serious nature.

Encephalography now revealed moderate dilatation of the ventricular system. There was asymmetry of the temporal horns, deformity of interpeduncular and pontine cisterns, and a midline suprasellar air cyst containing residual air after twenty-four hours. The distribution of subarachnoid air suggested microgyria and macrogyria. These changes in the cerebral cortex, associated with porencephalic cyst, ventricular dilatation, and abnormal cisternal outlines, suggested congenital developmental defects of the central nervous system (Fig. 4).

D. C.'s subsequent development has been as follows. At 2 years he was able to seat himself in a child's chair (2 years) and to walk upstairs one foot at a time (18 months), but he was likely to fall when hurrying (less than 18 months). At 2½ years he seldom fell, even when hurrying (2 years). At 3 years he walked upstairs with alternate feet, when holding the rail (3 years). At 3½ years his running was atypical; he ran on tiptoes, taking short steps, and leaning slightly backward, with knees bent and arms raised and tense. According to report, he appeared to fear high places, trembling all over when placed on the stationary tub at home. He has always been a cautious child who moved slowly.

His manual development has shown less retardation than in infancy. At 2 years he built a tower of six blocks (2 years) and turned the pages of a book (21 months). At 2½ years he built a tower of eight blocks (2½ years). At 3 years and thereafter attentional factors made the tests of manual coordination invalid. Although D. C.'s actual manual performance was up to age, his manipulation continued to be awkward.

Language development has been slow. At 2 years D. C. used four words (15 months), expressed himself jargonwise (15 months), and responded to such commands as "come" and "bring me. . . ." At 2½ years he spontaneously named the

pictures, "dog" and "shoe" (2 years), repeated any word said to him, and made such requests as "more" (2 years). At 3 years he put words together, "Me eat" and "Where Bob?" At 3½ years he named seven of the test pictures (3 years), placed the cube correctly in the cup, box, and plate on command, and used such language as "Where Daddy work?" or "Where Babo, school?" His articulation was difficult to understand.

Adaptively, he has, at each age, given one response considered normal for that age, but a response inconsistent with his general adaptivity. For instance, at 2 years of age he inserted the square in the performance box (2 years); but building the train, drawing a vertical line, and pouring the pellet from the bottle could not be elicited. At 3½ years he made a horizontal and vertical mark in response to the cross (3 years) but he did not always solve the three-hole formboard (2 years), and he failed to add a chimney to his train (2½ years). At 4 years he identified six geometric forms (3½ years), but he did not build the bridge (3 years).

Habit training has been slow. Self-feeding was learned by 3 years; complete toilet training, by 3½ years. The only atypical home behaviors reported are as follows. At 2 years, he banged his head and shook the bed at night; at 2½ years, he had a habit of holding his hands up over his ears; at 3½ years, he blinked and rubbed his eyes whenever in a strange place, and he feared high places.

Compared with Case 1, D. C.'s development has been less retarded, despite the fact that the roentgenologic findings are more abnormal. It is remarkable that a child whose brain shows as much pathologic involvement as D. C.'s does not present more abnormalities of behavior. It is significant that it was not until after encephalography that other observers could be convinced that the child was defective.

DISCUSSION

The two cases presented above illustrate the difficulty that may be encountered in establishing a diagnosis of cerebral abnormality. At the age of 4+ years (the time of this publication) both children, who are definitely defective, might appear normal to the casual observation of even a trained pediatrician. Yet psychologic examination showed the abnormality at 6 months, and both children give roentgenologic evidence of considerable cerebral involvement.

The establishment of an early diagnosis in these conditions is desirable for several reasons. The necessity of incorporating the psychologic examination as an integral part of the medical examination prior to adoption has been emphasized many times.[4, 8] Both of these children were prospective adoption candidates until the findings of the psychologic examination were available.

In any case of abnormal behavior the examination is no less important. The difficult task of educating parents to accept the fact that they have a defective child is made easier by the early diagnosis of the condition and by progressive disclosure of the diagnosis over a period of time. Thus false hopes are not engendered, and the parents are not led to "shop" in search of a cure.

Another consideration is the time and energy wasted in the handling of the problem. Both of the children discussed in this paper at times presented a picture which simulated regression of behavior in

response to environmental disturbance. In reality, the cause was fundamentally organic. By the correct diagnosis, costly psychiatric therapy was avoided. Psychometric study should precede psychotherapy, particularly in dealing with early childhood, when interpretation of child behavior from an adult viewpoint is hazardous.

Feeding problems are particularly deserving of psychologic study. Both of our cases were considered normal infants except for feeding difficulty.

Differential diagnosis, based upon the psychologic examination, is not a simple matter. Normal variation of behavior is great, and failure to measure up to norms is not necessarily abnormal. There are no criteria of behavior which are invariable indications of defect. Rather, it is the total behavior complex that must be studied and evaluated. Only a person with clinical experience with respect both to normal and abnormal development can appraise behavior, and even then (as in Case 1) one examination may not suffice. The observation of any atypical behavior merits re-examination.

As in the two cases we have cited, normal motor development is not necessarily an indication of normal mental functioning. Neither is abnormal motor development an indication of mental deficiency. The blind child with normal, or even superior, endowment sits and walks late.[9] He lacks the visual stimuli which promote ordinary postural growth. Reliance on postural development in infancy as an indication of normality is an inadequate basis of appraisal.

Admittedly, a neurologic examination in infancy is of limited value. Sachs and Hausman have emphasized the importance of determining the mental status of neurologic problems of infancy.[7] We reiterate that a behavior examination is an important aid to the diagnosis of central nervous system disease because, through its varied situations, it elicits both integrated and specific aspects of brain functioning.

SUMMARY

Two cases of cerebral abnormality have been described.

The existence of this condition, although not apparent in ordinary pediatric or neurologic study, was clearly indicated by routine psychologic examination at the age of 6 months.

The advantages of early diagnosis of cerebral abnormality have been discussed.

Psychiatric therapy should not be undertaken in a preschool child until his behavior has been adequately tested psychologically.

The fundamental weakness of any test based upon postural or motor performance alone as a measure of mental development is again pointed out.

Psychologic examination is advocated as an essential procedure in the evaluation of unusual feeding difficulty or other behavior disorders of infancy.

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NEURAL MATURATION AS EXEMPLIFIED IN ACHIEVEMENT OF BLADDER CONTROL

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THE proposition that sequential changes in behavior activities of the growing infant reflect different levels of neural organization should meet with no serious objection. The exact structural correlates corresponding to a particular phase of behavior development may not be known; the factors contributing to a reorganization of neural structure and function may transcend direct determination; nevertheless, the fact that neural development has taken place may be clearly indicated by the nature of changes in overt behavior.

The objectives of the present investigation were: (1) to determine the sequential changes in behavior which accompany and denote the development of voluntary control of micturition, and (2) to ascertain the effect of an early systematic training schedule upon the ultimate achievement of bladder control, that is, whether it accelerates, distorts, or is ineffectual in influencing the general course of development of this order.

Micturition is a convenient behavior to study as a basis for interpreting the development of neural organization because in the newborn infant it is a reflex activity presumably under the dominance of infracortical centers. As development proceeds, it assumes voluntary or deliberate qualities which undoubtedly reflect the influence of the cerebral cortex upon the reflex mechanism. Notwithstanding the complex character of the neural organization, involving as it does the sympathetic, the parasympathetic, and the central nervous systems, it is possible by the observation of overt behavior to ascertain the deliberate aspects of the activity. By determining the time and manner of achievement of these voluntary aspects, the basic behavioral changes are made available for more detailed correlation of structure and function.

EXPERIMENTAL PROCEDURES

The subjects of the study were two sets of identical twin boys, Peter and Charles Dalton and Hugh and Hilton Putney, who were in the laboratory five days a week, between 9 A.M. and 5 P.M. The age range during which the Dalton twins were being studied was from 23 to 470 days, and for the Putneys, from 41 to 800 days.

Empirically, it seemed that physiologic growth in the function of micturition would be reflected by an increase in amount of urine

From the Normal Child Development Study of the Department of Pediatrics, Columbia University, and the Babies Hospital.

voided at any one time and a decrease in frequency. It was also thought that such changes would be reflected in measurements obtained during a time-sample of seven or eight hours. In order to obtain these measurements, the babies were kept in their cribs one day a week. A glass vessel to which rubber tubing was attached was placed over the penis. The urine passing through the rubber tube was collected in a cup suspended in such a way that increased weight of the cup set up an electrical contact and rang a bell. In this way the time and frequency of micturition were accurately recorded, and the amount voided on each occasion was ascertained.

The other four days a week were devoted to the study of toilet training. During this time one member of each pair of twins, viz., Peter Dalton and Hugh Putney, was systematically placed on the chamber every hour. The negative or positive response to the chamber was recorded; records were also kept of the occasions when the children were found wet during the intervals. The other boys, Charles Dalton and Hilton Putney, were not allowed on the chamber until they were considerably older.

ANALYSIS OF THE DATA

It was expected that data accumulated once a week to determine the amount and frequency of micturition would reveal a tendency toward reduction in frequency and an increase in amount voided at each occasion. That such was not the trend is illustrated by the series of curves in the case of Hugh Putney. Curve A of Fig. 1 shows the average amount voided at each occasion plotted against the chronologic age. Curve B of the same figure indicates the average interval between voidings, and Curve C shows the amount voided per unit of time. A running mean has, for convenience, been drawn through the data. The scatter around the means is so great that these measures cannot be considered an accurate representation of growth trends in physiologic function or bladder capacity. A similar scatter was demonstrated in the records of the other children. The data obtained from members of each pair of twins showed marked similarity, despite differences in their programs on the other four days of each week. Even this correspondence in the records of twin pairs cannot be taken as evidence that the measurements represent growth in bladder capacity, since it may have been influenced by similarity of other conditions, such as eating and sleeping schedules.

That slowly increasing capacity must accompany growth in anatomic size may almost be assumed as self-evident. That the influence of steady growth is not revealed clearly by the data in Fig. 1 can only mean that other systematic causes of variability have operated to a degree which effectively obscures the influence of growth in size. Many possible causes of variability have been recognized and dis-

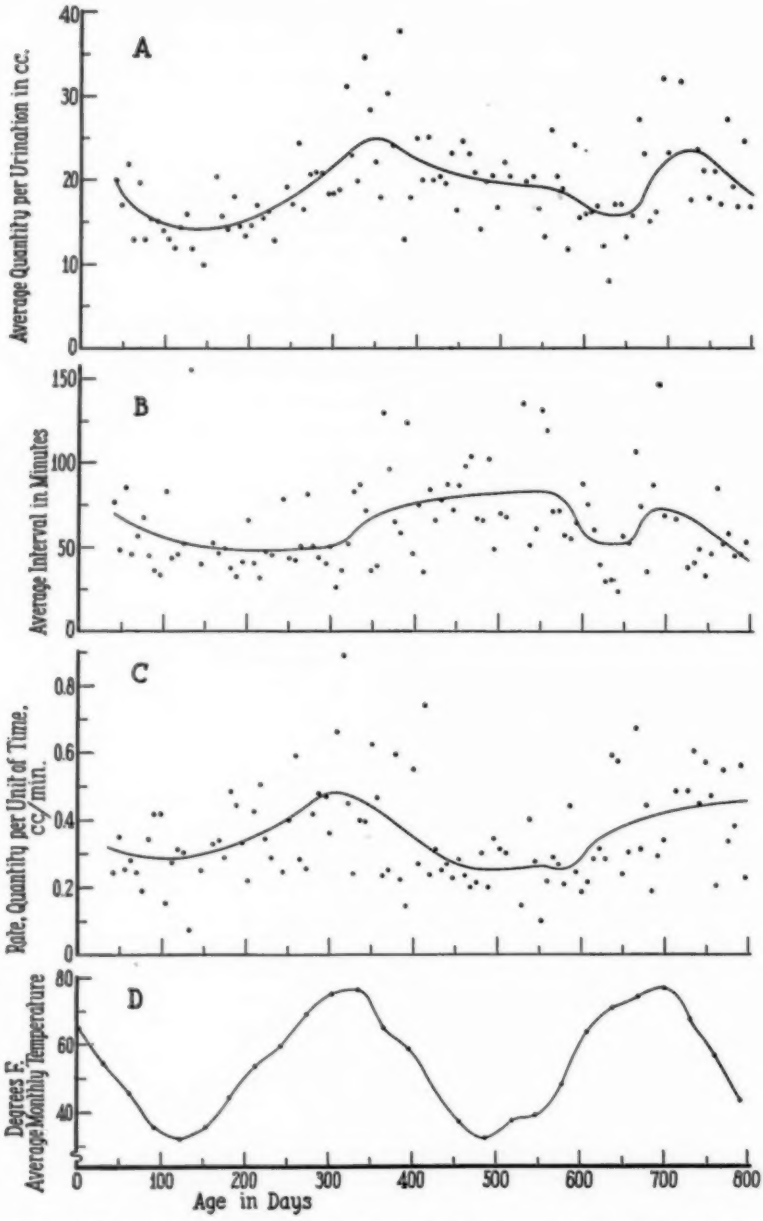

Fig. 1.—The first three curves show for Hugh Putney (*A*) the average amount voided on each occasion, (*B*) the interval between voidings, and (*C*) the rate, or amount voided per unit of time, as obtained one day a week over a period of two years. Curve D indicates the average monthly temperature for the vicinity.

cussed in contemplating these data; in most instances accurate appraisal of importance has not been possible. The vicinity temperature* (Curve D) has been included in Fig. 1 as one determinable factor influencing the data. The parallel course between Curve D and the other curves through certain age periods suggests the wholly reasonable conclusion that the child was given a larger volume of liquid when the weather was hot than at other times. It seems, therefore, that twenty-four-hour specimens plus accurate determinations of fluid intake are indispensable to a study of development in bladder capacity. Even then it may be that the whole neurophysiologic mechanism is so complex that various components cannot be sufficiently isolated to determine growth in organ capacity per se.

While the data obtained on the twins are inadequate to draw any conclusions concerning development in physiologic capacity, they do serve to cast doubt on the alleged functioning of a physiologic rhythm, even in the earlier months. A scattergram of the number of voidings by Hugh Putney during each hour of the day for the first 300 days of

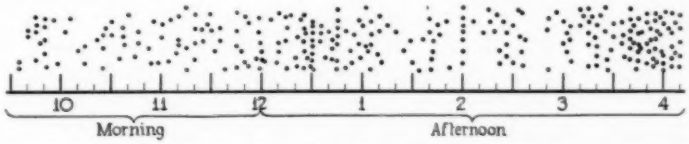

Fig. 2.—A scattergram shows the number of voidings by Hugh Putney during each hour of the day for a period of ten months.

life fails to exhibit a definite rhythmic tendency (Fig. 2).† Attention is drawn to this doubt concerning a rhythmic trend because so often the recommended method of training calls for conditioning of the basic physiologic rhythm. The striking correspondence in the records of each pair of twins does indicate that the four-day training schedule imposed upon one member of each set did not influence the behavior appreciably on the days when urinal tubes were worn.

The data bearing upon the child's response to toilet training are more informative. A measure of achievement was calculated by plotting against chronologic age the ratio between positive responses to the chamber and total number of urinations during the seven hours of each day. This ratio has been called the *success factor* and is shown in the curves of Fig. 3. A declining trend in the percentage of positive responses to the chamber is indicated in the curves for both Peter Dalton and Hugh Putney after the first few weeks. The period when they were least responsive to the toilet situation was between the age of from 6 to 10 or 11 months. From about 320 to 360 days there

*Data obtained from the United States Government Weather Bureau.

†Although there is some congestion of frequencies around midday and late afternoon, these incidents can be explained on an environmental, as well as a physiologic, basis.

occurred a rapid increase in the success factor. The observations on the Dalton twins were terminated when they were 470 days old, so that a decline following this initial spurt in improvement is suggested though not clearly demonstrated. That a decline was actually in progress is borne out by the curve of Hugh Putney. When the Dalton twins were 430 days old, after Peter had begun to show a period of appreciable improvement, toilet training was initiated with his brother

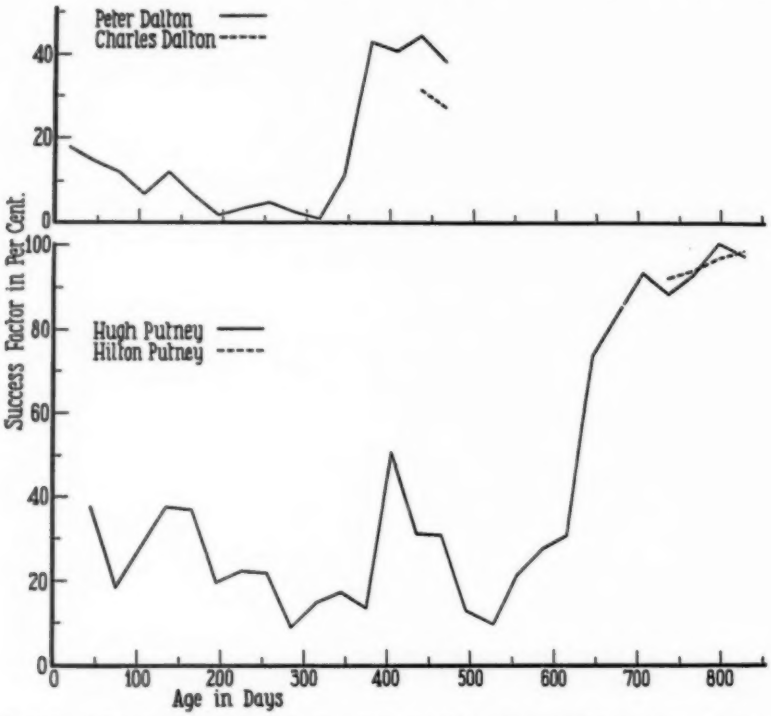

Fig. 3.—Achievement curves indicating the percentage of successful responses to the toilet situation as manifested by all four children.

Charles. Even at the beginning Charles' success rating is only 10 per cent below that of his twin, who since the age of 23 days had been given the opportunity to associate the chamber with voiding.

The curve of Hugh Putney shows a second rapid rise shortly after he was 530 days old; by the time he was 2 years old he was stabilized within the ninetieth percentile. At the age of 2 years, his twin, Hilton, was exposed to the training schedule. Even at the start, Hilton's achievement was slightly above that of his twin who, from the age of 41 days, had been subjected to systematic training. The hourly training schedule was continued with both children for four months,

a period long enough to indicate that Hilton, as well as his brother Hugh, was stabilized within the ninetieth percentile. There is no evidence that this result was influenced by happenings when the children were not in the clinic. Throughout the first two years the mother cooperated by withholding any training of Hilton when he was at home. In the clinic, however, although he was never allowed to use the chamber, he did have occasion to observe other children urinate in a vessel.

Separate studies by Tilney[1] and Conel[2] on the structural development of the human brain indicate that no part of the cortex is functioning appreciably at the time of birth. Cystometric studies by McLellan[3] offer additional evidence that the part of the cortex governing micturition is not functioning in the infant even as late as 6 months of age. This investigator observed uninhibited reflex activity of the detrusor urinae in six infants ranging in age from 2 to 6 months. In making the cystometric examinations it was noted that rhythmic contractions during the fill are common to infants of this age range. Similar contractions were observed in adult patients suffering a supranuclear lesion; moreover, these patients exhibited a type of micturition simulating that of the infant. In contrast, the type of micturition shown by patients with lesions in the lower centers in no way resembled the infantile reflex. Therefore, rhythmic contractions during the fill and an infantile type of micturition were considered to indicate the absence of inhibitory influence from the cerebral cortex. In the light of these considerations, it can be assumed with reasonable certitude that the cerebral cortex exercises no influence upon bladder functioning of the newborn infant.

In view of the evidence that cortical centers are not functioning in the young infant, the relatively high level of the achievement curves of both Peter Dalton and Hugh Putney during the early weeks warrants consideration. It might be contended that a certain amount of "conditioning" of the reflex mechanism takes place at an infracortical level. On the other hand, it is known empirically that any mild stimulation is likely to activate voiding in the young baby. It seems reasonable to assume that the necessary handling of the baby in preparation for the chamber provided the requisite stimulation for "catching" a few specimens and raising the success factor during the early weeks. This slight elevation of the achievement curves suggests merely that the reflex mechanism governing micturition in the newborn infant is hypersensitive. The decline in the curve which follows is interpreted as an indication that the reflex mechanism had become less sensitive to vicarious stimuli, but that specific association with the situation was not evident. It may be that the loss of sensitivity of the reflex mechanism represents an inhibitory influence of higher centers upon the *reflex activity* per se, since, from other studies[4, 5] of neuromuscular

development, a diminution of reflex activity is one of the earliest indications of cortical development. This type of inhibition should not be confused with voluntary inhibition of micturition which develops much later.

The sharp rise in the curve between 10 and 12 months corresponds to the onset of cortical participation in the function and the association of the act with a particular situation. It has been observed that the rise in the success curve occurs about the time the child begins to pay unmistakable attention to the act of voiding and to the result. It is at this time that he may be found playing in the puddles or in other ways indicating an association of the act with the specific situation; he may listen to the sound, or even a glint in the eye may reveal his awareness of the act. It is possible that this period corresponds to the maturation of cerebral sensory centers which denote bladder sensibility. There is probably some, although incomplete, development of cortical centers of the motor areas governing sphincteric action. It is interesting that this period occurs at about the time that signs of cortical participation in movements involving other muscles in the region of the pelvis and lower extremities are evident.[6] This parallel development further suggests that some cortical control of the sphincters may be gained at this time.

There is a definite decline in the achievement curve following this first manifestation of cortical participation. From observations of general behavior the decline appears to correspond to a period of rapid advancement in associational behavior and the inception of discriminative and generalizing powers. This decline in the achievement curve warrants special emphasis. It is not, in the opinion of the investigator, an incidental phenomenon, but represents a phase inherent to the process of development. During the period of transition from simple direct associations to more complex, discriminative processes, the original associations are often interrupted. This temporary loss of a definite association as the ability to generalize develops has been observed in connection with other types of behavior.[7]

The subsequent sharp rise, which occurred in the case of Hugh Putney around 20 months and was stabilized around 24 months, indicates the actual functioning of the maturing powers of discrimination and generalization; that is, the ability to generalize and discriminate becomes integrated with the act of micturition. The child begins to learn that it is not merely a particular vessel, but a *kind* of receptacle or situation, that is suitable for voiding. It is at this time that the child may point to the vessel or in other ways take some initiative in indicating his desire.

Under ordinary circumstances there is probably another regressive phase after the child has begun to articulate and take the responsibility for excretory needs. The conditions of this investigation (viz.,

exposure to the toilet situation at hourly intervals) were such that the child was never called upon to exercise his own responsibility. With other children it has been observed that they accept the responsibility confidently for some months, but as their horizon of interest widens, there again comes a time when they verbalize the need immediately after the act rather than before. The regression at this later stage appears usually when the child shows a beginning tendency to engage in fantasy and other signs of mental activity concerned with things outside the realm of the immediate. At the inception of development in projective and retrospective mental processes of this order, the child is unable to bring all of the newly-developed cortical centers into timely and well-integrated functioning. A regression of this type does not reflect retarded maturation of the urinary system or of those neural centers which operate in its control, but rather the lack of integration of the newly-acquired cortical functions with the cortical centers controlling micturition. Subsequently, the ability to integrate multitudinous and remote interests with physiologic responsibilities is established. Emphasis is made of these regressive phases because socially and pedagogically they are the most troublesome and the least understood periods.

TOILET TRAINING

Current theories and practice concerning the best method of training the young child to achieve bladder control vary considerably. Some authorities recommend the induction of a training schedule during the early months. Following a study of groups of children, Scoe[8] says: "Training for bladder control may be begun as early as the third month. Since infants left untrained after the seventh or eighth month are conditioned with difficulty to the use of the toilet, it is important that training be started during the first six months of life, even if such training cannot be conducted in a highly systematic manner." Blatz,[9] despite his caution against overtraining, suggests that, up to the age of 6 months, the child should be placed on the toilet on rising, after meals, bathing, morning and afternoon naps, and at bedtime in order to acquaint him with the essentials of a voluntary process. Some of the more recent publications warn against the introduction of a training schedule too early. Aldrich[10] stresses the importance of waiting "for the necessary degree of development" and suggests that the time is probably ripe when the child is able to balance firmly on his legs. Gesell and Ilg[11] have wisely proposed certain behavior symptoms as a basis for judicious training: "Early training should be undertaken with moderation, without zealousness and also without solicitude. The mother may take note of the natural rhythms of micturition and of the times of the day when he responds most promptly to a routine toilet placement. The mother should especially

watch for the time when he wakes dry from his nap. This is one of the truest indications of a maturing ability to withhold micturition. It may occur during the last quarter of the first year, but usually is not established before 13 or 15 months. When the capacity to withhold has been attained, the response to the toilet usually is immediate, and a previously resistant child becomes compliant to the situation. At this same period the infant shows more awareness of wetting and of the puddles that he produces on the floor. This is a new level of discrimination and gives him a new chance to learn. He has first to know that he has urinated before he can tell that he is going to urinate."

Although there exists difference of opinion concerning the optimum time for the introduction of a training program, there is general agreement among many writers[9, 12-16] that the training schedule should be based upon the child's own physiologic rhythm. The assumption that the baby shows a rhythm of periodicity in voiding implies that it would be reasonable to expect micturition to occur at fairly regular intervals over a period of time. Such intervals would presumably show regularity with respect to the clock or the sleeping or the feeding schedule. The data obtained from the four children in this study fail to reveal any tangible evidence of regularity of this order which could be used as a guiding principle in formulating a training program.

Concerning the inception of a training program, the results of this investigation indicate that early toilet training is, to say the least, futile. The small percentage of successful responses to the chamber which may be obtained during the first few months is misleading, as it probably reflects hypersensitivity of a reflex mechanism and not true "conditioning" or association with the situation. It is preferable to postpone training until evidence of cortical participation in the act of micturition is manifested. This stage can be detected in the behavior of most children by the obvious attention they give to the act and to the result. The child probably suffers no handicap in the achievement of bladder control if training is delayed beyond the onset of cortical participation, i.e., until cortical control of the act is fairly well established. This statement is substantiated by the record of Hilton Putney. One reason for recommending the introduction of a training program at the inception of cortical participation rather than delaying until cortical control is established is to relieve the toddler of diapers. Furthermore, it is desirable to particularize the act of micturition at this stage in order to encourage the exercise of the newly-acquired sensory-motor experience. However, if training is initiated at this time, it should be done with the understanding that a period of decline or regression in the successful responses to the situation may follow before cortical control of the activity is stabilized. This period of regression may extend over several months.

If it is recognized that periods of regression are a part of the process of growth and that they coincide with rapid advancement in other aspects of development, then it is possible to handle them more judiciously.

No mention has been made of nocturnal control over micturition because that phase of development was not included in this investigation.

SUMMARY

Two sets of identical twin boys were under intensive study during seventeen and twenty-eight months, respectively, for the purpose of determining basic behavior changes accompanying voluntary control of micturition. Such an analysis of behavior development offers a foundation for a more detailed correlation of structure and function when the underlying neural mechanisms have been established. A second purpose was to ascertain whether or not a systematic "training schedule" appreciably alters the course of development. To this end, one member of each pair of twins, after the first month of life, was subjected to a program of being placed on the chamber at hourly intervals during seven hours of the day. Their twins were not allowed on the chamber until they were 14 and 24 months of age, respectively, at which time they were exposed to the same schedule of toilet training. In both cases the achievement of these boys approximated that of their brothers, even at the onset of their training schedule.

The achievement records of the two children who were given systematic "training" indicate that there are several distinct phases in the attainment of bladder control and that these phases are not altered by the imposition of a training program. During the early months of life the reflex is so hypersensitive that any mild handling or disturbance of position may initiate voiding. Subsequently, the reflex is less sensitive to vicarious stimuli. This period is represented in the achievement curve by a decline in the percentages of successful responses to the toilet situation. The onset of cortical participation is indicated by a sharp rise in the achievement curve and is reflected in the child's behavior by unmistakable signs of awareness of the act and the result. This rise in percentage of successful responses is a transient one; a regressive phase follows which apparently coincides with a period of rapid advancement in complex mental processes involving not only simple associations but discrimination and generalization. As these processes advance to a stage of functional integration with other activities, there occurs a second rapid rise in the achievement of bladder control. After this period the child's performances are stabilized at a fairly high level. However, there may be other minor regressive phases; an explanation of these has been proposed, although the conditions of this study precluded their manifestation.

A discussion of the optimum time to introduce toilet training has led to the suggestion that it be delayed until the child's general be-

havior indicates cortical participation in the act of micturition. Even then, periodic regressive phases are to be expected. Such regressions are temporary and apparently coincide with rapid advancement in other aspects of development.

Measurements of the frequency and the amount of voidings during one day of each week yielded no evidence of a basic physiologic rhythm which could be used as a guiding schedule in setting up a training program.

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EQUINE ENCEPHALOMYELITIS (WESTERN TYPE) IN CHILDREN

Report of Cases With Residual Atrophy of the Brain

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SINCE Meyer's[1] report of 1932, the virus of equine encephalomyelitis has been linked to outbreaks of acute encephalitis in man in various parts of the United States; some of these were due to the eastern, others to the western, strain of the virus. Reports, mostly of fatal cases, have appeared from time to time, but the late and residual effects of this disease have not received much attention. Recently we have seen two patients in whom a diagnosis of equine encephalomyelitis (western strain) could be made. Both of these patients presented permanent cerebral damage as a result of the disease. Résumés of their case histories are presented below.

REPORT OF CASES

Case 1.—E. U., a 2½-month-old female infant, became ill on Aug. 20, 1939, with a sudden onset of fever and convulsions. She was born June 7, at Modesto, Stanislaus Co., Calif., which is in the San Joaquin Valley where equine encephalitis is prevalent. The birth was spontaneous. The patient was the second and smaller of twin girls. Her weight at birth was 5 pounds 9 ounces. On breast and supplementary feeding she gained well and seemed perfectly normal and equal to her twin before the onset of the present illness. With the onset of convulsions she was taken to her local physician who found only a mild pharyngitis and a temperature of 103° F. However, because of fever and persistent convulsions which at first occurred every hour, she was placed in a hospital in Modesto on the third day of illness and two days later, August 25, was transferred to the Children's Ward of Stanford University Hospital where we first saw her. Fluoroscopic examination and lumbar puncture were performed in Modesto and were said to show nothing abnormal. On entry the infant seemed well developed and fairly well nourished, but she was quite lethargic and the cry was feeble. A convulsion occurred at the time of admission, characterized by generalized spasticity with opisthotonus and twitchings of the muscles of the face; it was followed in five minutes by relaxation and sleep. Physical examination disclosed an infant weighing 4,230 Gm. The head was symmetrical; both the anterior and posterior fontanels were open, the former quite widely so, but there was no bulging or depression. A slight elevation of the parietal over the occipital bone was noted. Examination of the eyes, ears, nose, and throat disclosed no abnormalities. The neck was held stiff and resisted flexion. The heart, lungs, and abdomen revealed no abnormalities. The extremities were normal. The tendon reflexes were equal but hyperactive; Babinski's sign was negative. The laboratory work disclosed a mild secondary anemia and a leucocytosis; erythrocytes, 3,800,000; hemoglobin, 65 per cent (Sahli), or 11 Gm. per cent; leucocytes, 21,000, with polymorphonuclears,

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44 per cent, and lymphocytes, 54 per cent. The results of urinalyses, tuberculin tests (including a test with 1.0 mg. of O.T.), Wassermann and sedimentation tests were all normal. The spinal fluid was clear and under no increased pressure, but it contained eighty cells per cubic millimeter, all lymphocytes. Protein was 740 mg. per cent; sugar, 39.2 mg. per cent; and the colloidal gold curve was 12111112221. Smears, cultures, and guinea pig inoculation of the spinal fluid failed to reveal any organisms. Roentgenograms of the chest and long bones were interpreted as normal. On September 3, blood was sent to the Hooper Foundation of the University of California for virus neutralization tests; this was reported by Miss Beatrice Howitt as positive for the western strain of equine encephalomyelitis virus.

On admission the infant had a rectal temperature of 38.9° C. (102° F.), which promptly dropped to normal on the same day and was never again above 38° C. Treatment was symptomatic and consisted of a transfusion of 125 c.c. of citrated blood and gavage feeding for the first five days, after which there were no more convulsions and the infant was able to nurse from the bottle. Lumbar puncture, which was performed without difficulty on the day of admission, was attempted without success on August 29, 30, and 31; a small amount of clear fluid was again obtained on September 5. On September 7, 1939, the baby was dismissed to the care of her parents. By this time it was noticeable that the child could not follow objects or light.

On Oct. 27, 1939, she returned for further examination because the local physician had noted an apparent overlapping of the bones of the cranial vault for the past two weeks and because there had been a recurrence of convulsions on October 23.

Since the onset of her illness, she had not kept pace in mental development with her twin. Examination showed the general state of nutrition to be good, the weight being 5,710 Gm. The circumference of the head was 38 cm., and of the chest, 41 cm. The body length was 58 cm. The head looked small, and there was marked elevation of one cranial bone over the adjoining one at the occipito-parietal suture, at the sagittal, and at the coronal sutures. The posterior fontanel was closed; the anterior, small and somewhat depressed. There was no response to visual or auditory stimuli, although examination of the fundi and ears revealed no visible abnormalities. The lower extremities were hypertonic with bilateral ankle clonus and positive Babinski reflexes. On lumbar puncture only 1.5 c.c. of fluid could be obtained; it showed 12 lymphocytes and 530 erythrocytes per cubic millimeter; the Pandy test was +++. As it was impossible to obtain more fluid from either lumbar or cisternal puncture, air encephalography could not be done as had been planned. A sample of blood on October 28 was again reported by Miss Howitt as positive for antiviral substance against equine encephalomyelitis virus, western strain.

On October 29 the infant was again dismissed to the care of her parents. The diagnosis was encephalitis due to equine encephalomyelitis virus (western strain) with postencephalitic atrophy and mental deterioration, including blindness and deafness. She seems to be destined to a life of imbecility.

CASE 2.—A. M. was referred to us from the Shriner's Hospital for Crippled Children in May, 1939, at the age of 4 years, for an intelligence test and speech examination. He was born April 15, 1935, at Sanger, Fresno County, Calif. The birth was normal, and the birth weight was 6 pounds 9 ounces. He had been normal in all respects before the onset of illness, which began in July, 1935, at the age of 3 months, with an attack of convulsions accompanied by fever and diarrhea. The temperature returned to normal after a week, but the diarrhea persisted for three weeks, and the convulsions which occurred two or three times a day were followed by paralysis of the left side of the face and body. The

facial paralysis had disappeared six weeks later. Movement of the trunk and extremities improved, but the left arm has remained permanently spastic. A week before the onset of the patient's illness, his sister, then 2 years of age, had an attack of convulsions and diarrhea from which she recovered without complications or permanent disability after two weeks. The third member of the family to become ill was the father, aged 44, who also had symptoms of a gastroenteritis, which was followed by a weakness of one leg; this gradually cleared and is no longer noticeable. Following his illness, the infant developed very slowly; sitting was delayed till the age of almost 1 year; he walked at 20 months, and did not talk until 2 years of age. At 4 he still could speak only single words or isolated phrases. Convulsive seizures had been noted at 9 and 12 months of age and thereafter two or three times a year. In 1938-39 he was an outpatient at the Shriner's Hospital, where corrective braces were applied to the paralyzed left arm to bring it into a more useful position. After examination in our clinic he was referred to the hospital for observation on June 12, 1939.

Examination disclosed a small thin boy in no distress, with a blank, expressionless face; he responded to commands, and occasionally he would say a few simple words, such as "go home." Significant physical findings were confined to the extremities. The left leg was found to be thinner and 1 cm. shorter than the right. The left arm was spastic and held in two-thirds flexion with the fist clenched. Movements of the other extremities were normal. Results of routine laboratory examinations, including blood count, urinalysis, blood Wassermann test, tuberculin and erythrocyte sedimentation rate, showed no significant abnormalities. The spinal fluid was clear with no cells and a normal sugar (67 mg. per cent) and protein (34 mg. per cent). The colloidal gold curve was flat, 111100000. X-rays of the skull and air encephalograms were reported as normal. It was the opinion of our speech clinic that he had an "anarthria of an organic nature due to a lesion of speech centers." A mental examination disclosed a mental age of 15 months (actual age, 50 months) and an I. Q. of 30. The diagnosis was imbecility. A sample of blood sent on June 15, 1939, to the Hooper Foundation was found by Miss Howitt to neutralize the virus of equine encephalomyelitis (western), but was negative against the virus of St. Louis encephalitis.

DISCUSSION

We have described two cases of equine encephalomyelitis in infants, shown to be due to the western strain of virus by the presence of neutralizing antibodies in the blood. In both instances the acute illness began in early infancy (at the ages of 2½ and 3 months) and was followed by convulsive seizures and mental retardation. The first patient was seen during the initial illness, and the second, some four years after a similar episode. Case reports of equine encephalomyelitis in human beings are not numerous, and in some of the reports the diagnosis has not been confirmed either by the isolation of the virus itself or by the demonstration of antiviral substance in the blood. That the latter persists for a long time after the acute illness is evident from our second case and has previously been reported by Howitt.[2] Table I lists the cases of equine encephalitis, or the suspected cases, that have been reported in the United States, both for the eastern and the western strains of the virus. Apparently the mortality rate for the eastern strain is higher than for the western, and a majority of cases of the

TABLE I

REPORTS OF EQUINE ENCEPHALOMYELITIS IN MAN (SUMMARY)

AUTHOR	TOTAL CASES	CASES IN CHILDREN	VIRUS ISOLATED	NEUTRALIZATION TESTS	DEATHS	RESIDUAL DEFECTS
Western Strain						
Howitt[2]	32	8	2	30	2	4
Eklund and Blumstein[4]	6	?	0	1	2	Not mentioned
Breslich and co-workers[5]	23	4	0	4*	5	Not mentioned
Eastern Strain						
Wesselhoeft and co-workers[8]†	8	7	4	0	8	--
Jakmauh and Feemster[11]	34	24	9	10	15	Not mentioned

*One additional case positive for St. Louis virus.

†Cases reported by Webster and Wright[9] and by Fothergill are also included in the series by Wesselhoeft and associates and are not tabulated twice.

former occur in children. None of the eastern reports specifically records any residual effects in the recovered cases, although Olitsky,[7] writing in Brennemann's *Practice of Pediatrics*, states that "sequelae may occasionally occur after recovery from the acute phase of more virulent attacks of the infection." The largest and most completely tested group of cases due to the western strain is found in the report by Howitt,[2] in which the virus or its neutralizing antibodies were demonstrated in every instance. The original note on equine encephalomyelitis in man by Meyer,[1] as well as the recent report by Larimer and Wiesser,[3] contains no etiological proof of the virus. The cases in these two reports, therefore, have not been included in the table. Eklund and Blumstein[4] were able to demonstrate neutralizing antibodies for the western strain in only one of three recovered cases, and Breslich and his associates[5] found neutralization of western equine encephalomyelitis in four and of the St. Louis virus in one of the six patients tested. In Wynns and Hawley's analysis of epidemic encephalitis in California,[6] there were 81 cases of the 102 which did not show neutralization for the St. Louis virus; the authors presumed, without specific tests, that many of these cases may have been due to the equine encephalomyelitis.* Permanent injury from the disease was mentioned in one of Meyer's cases, an adult, and in four of Howitt's series, all of whom were children. Permanent effects included convulsive seizures, muscular weaknesses or paralyses, and mental defects. Fourteen of sixty-two patients whose cases Wynns and Hawley could follow had some disability, including one with internal hydrocephalus; however, as mentioned above, it is not known which, if any, of their cases were actually due to equine encephalomyelitis.

*Since it has been shown by Howitt[2] that the viruses of St. Louis encephalitis and of the western strain of equine encephalomyelitis have both been responsible for human cases of encephalitis in the same areas in California, it is important that neutralization tests for both of these viruses be carried out before a definite etiological diagnosis can be made.

It is as yet impossible to say how frequently residual damage to the central nervous system from equine encephalomyelitis infection occurs. From the cases reported here and from the literature reviewed, it is apparent that these permanent and disastrous aftereffects are not uncommon. It is possible that infants and young children are particularly susceptible to them.

Case 1 is of special interest because the extreme cerebral atrophy, occurring in an infant whose cranial sutures were not yet interdigitated, caused a contraction of the cranial vault that was palpable and visible along the suture lines. Such a manifestation is decidedly unusual and has not, so far as I am aware, been previously described.

SUMMARY

Two cases of equine encephalomyelitis (western strain) in infants are reported. Specific antiviral substance was demonstrated in the blood in both. Both cases presented permanent nervous sequelae as a result of the infection. These consisted of cerebral atrophy with overlapping of the cranial bones, mental deterioration, and apparent blindness and deafness in the first patient; mental deterioration with partial hemiplegia and speech defect in the second. Reports of other cases in the literature are reviewed and tabulated.

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IDIOPATHIC LIPEMIA WITH SECONDARY XANTHOMATOSIS, HEPATOSPLENOMEGALY, AND LIPEMIC RETINALIS

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DURING the period of hospitalization of a 1-year-old infant, a routine sample of blood serum taken for a Wassermann test was found to be creamy white in color. An attempt was made to determine the etiology of the lipemia. Cases of lipemia in children, with and without xanthomatosis, for which no cause was found, have been reported by several investigators.[1, 3-5]

W. R., a 1-year-old white boy, was brought to the hospital on April 10, 1939, because of a persistent purulent discharge from the left ear of four weeks' duration and a failure to gain weight. The family history was negative. Father, mother, and four siblings were living and well. There was a history of one stillbirth, and one infant died of pneumonia at the age of 3 months. The birth was full term and normal, the patient weighing 7 pounds. Prenatal diet was adequate. The patient was breast-fed for two weeks and then placed on a formula of whole milk, water, and Karo. At entry he was receiving one quart of milk plus three teaspoonfuls of cod-liver oil daily. No cereal, orange juice, egg, or vegetables were included in the diet. On admission, the patient was unable to sit up without assistance, nor was he able to crawl about. He appeared mentally alert. There were no previous illnesses except for a persistent mucopurulent discharge of six months' duration. No history of colic was obtained.

Examination revealed a fairly well-developed but poorly nourished white male infant weighing 15 pounds, who did not appear acutely ill. Temperature, pulse, and respiration were normal. The skull showed prominent frontal bossae. The anterior fontanel admitted one and one-half fingers; the posterior one was closed. The skin was moist, elastic, and clear except for an area of ammoniacal dermatitis around the buttocks. The tonsils were enlarged. On the upper palate there were a few discrete whitish yellow papular lesions. There were no teeth. A profuse bilateral purulent nasal discharge was present. The right eardrum was retracted, and thick yellowish green pus filled the left auditory canal. There was no postaural swelling. The costochondral junctions were enlarged. The lungs were normal, except for a few transient râles at the bases. Examination of the heart, abdomen, and genitals was negative. The liver and spleen were not palpable. There were no abnormal neurologic findings.

The following laboratory data were obtained. Hemoglobin was 71 per cent (Sahli); red blood count, 4,450,000 per cubic millimeter; white blood count, 13,600 per cubic millimeter, with polymorphonuclear cells, 52, lymphocytes, 40, mononuclear cells, 7, and eosinophiles, 1. The red blood cells were normal in shape, size, and color. Examination of the urine was negative. The blood sugar was 100 mg. per 100 c.c. blood; blood nonprotein nitrogen, 26 mg. per 100 c.c. blood. The Schick, Dick, and Mantoux tests were negative. Nasal culture revealed *Strepto-*

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coccus hemolyticus, Bacillus influenzae, and *Micrococcus catarrhalis.* Ear culture showed *Staphylococcus aureus, Streptococcus hemolyticus,* and *Bacillus influenzae,* and throat culture, streptococcus and pneumococcus. X-ray examination of the chest showed no abnormalities. The sinuses were cloudy, consistent with infection, and the long bones showed no pathologic changes.

During the patient's stay in the hospital, an adenoidectomy was done, and the aural discharge gradually subsided. The nasal discharge was refractory to therapy and subsided after two months of heliotherapy and nasal irrigations. The child was given an adequate diet and gained 2 pounds while in the hospital.

A routine blood Wassermann test was made which showed gross evidence of lipemia. A fasting blood sample showed an elevated level of total fatty acids of 1,900 mg. per cent. Before further investigation could be carried out, the mother requested that the child be discharged.

SECOND ADMISSION

The patient was readmitted two months and two weeks later because of a progressive yellow papular skin eruption involving buttocks, chin, eyelids, ears, and mouth. He had been doing well at home and weighed 19 pounds. His appetite was good, his diet consisting of one quart of milk daily, cereal, eggs, vegetables, orange juice, and cod-liver oil in adequate amounts. Four teeth had developed, and he was now able to sit up and stand with support. The rhinorrhea and otorrhea had not recurred.

Physical examination revealed a well-developed and well-nourished infant. On the buttocks there were approximately twenty discrete, circular and oval papular lesions of a yellow color with an umbilicated top, measuring from 2 to 6 mm. in diameter. Similar lesions were found on the thighs, scrotum, and ears. Those on the eyelids were reddish yellow and resembled chalazia. On the hard palate there were many small yellow papules. (Figs. 1, 2, and 3.) The liver and spleen were palpable two fingerbreadths below the costal margin. The ophthalmologic service reported that the eye ground findings were consistent with the picture of lipemic retinalis.

At the end of the first week there was no change in the appearance of the lesions. The patient was then placed on a low fat diet consisting of skimmed milk, vegetables, bread, and stewed fruits. Cod-liver oil and butter were eliminated completely. Within a period of one month the lesions on the buttocks, scrotum, and chin gradually cleared. The lesions on the upper palate were still present but fewer in number. The spleen decreased in size and was not palpable at the time of discharge. Associated with this improvement, blood studies revealed a diminution of the total fatty acids from 3,115 mg. per cent to 1,311 mg. per cent. Grossly, the blood maintained its creamy white color.

During the first week of hospitalization, a biopsy of the skin lesions was taken, and the pathologic report stated that foam cells were present in the corium. (Fig. 4.)

DISCUSSION

Physiologic lipemia follows the absorption of intestinal fat, and the degree of lipemia depends upon many factors, especially the rate of absorption from the intestines into the blood stream and the rate of elimination.[6] Van Slyke believes that lipemia is produced when the body is lacking in, or unable to utilize, carbohydrates, as in fasting or malnutrition, resulting in a call upon the fat depots to supply fuel.[7]

Fig. 1.

Fig. 2.

Fig. 3.

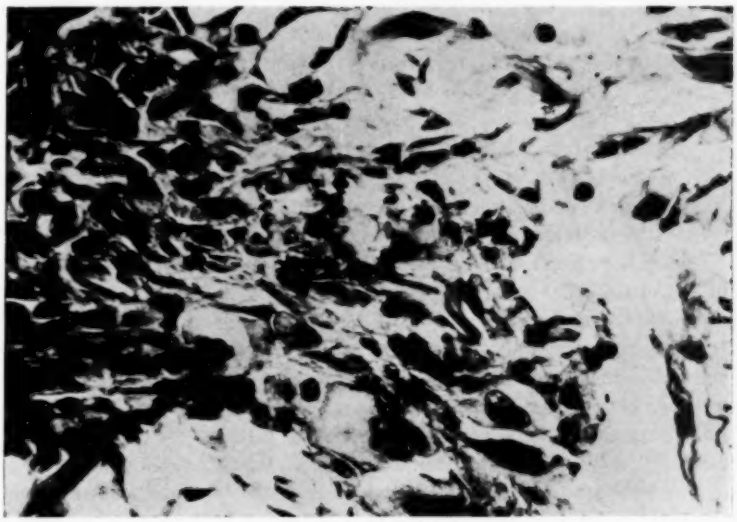

Fig. 4.—Pathologic report: "Corium infiltrated with large foam cells. In one area these cells form a nodular thickening of the tissue. Polymorphonuclear leucocytes in moderate numbers infiltrate the tissues of and around this nodular thickening. Consistent with so-called xanthoma."

The physiologic factors which control fat metabolism are still undetermined. There are nervous and hormonal factors which may control fat deposition and utilization. Mansfield and Muller[8] found an increase of fat in denervated muscle and concluded that the percentage of muscle fat is normally influenced by two sources, namely, the nervous system and the blood. This was confirmed by Hausberger,[9] who severed large branches of the mixed nerves supplying the interscapular fatty body and found that this denervated area contained more fat than did the normal. The relationship between the sympathetic system and fat utilization was experimentally studied by Beznak and Hasch.[10] They found an increase of perirenal fat after splanchnicotomy and concluded that, when connective tissue is deprived of its sympathetic supply, there is a slowing down in the mobilization and deposition of fat. DeLangen[11] found that the lipemia produced by administering barbiturates in doses sufficient to produce sleep could be abolished by section of the spinal cord at the level of the third thoracic vertebra.

Many attempts have been made to correlate the various hormones with the discharge and transport of fat into the blood stream. The pancreatic hormone, lipocaic, prepared by Dragstedt and co-workers,[12] is believed by them to play a role in the utilization of fat in the liver. Holt used lipocaic in a patient with idiopathic lipemia, but he found that it had no effect upon the blood lipid level. Further studies concerning the action of the pancreas on lipid metabolism were made by Entenman, Chaikoff, and Montgomery,[13] who produced complete obstruction of the pancreatic duct in dogs. They found that the fall in blood lipids could be controlled by the administration of pancreatic juice, and they believed that this fall resulted from the lack of a factor, or factors, derived from the external secretions of the pancreas. Wertheimer[14] has shown that insulin has no effect upon lipemia, except in those cases where it is secondary to disturbances in carbohydrate metabolism. There is still no definite evidence that either internal or external pancreatic secretions influence lipid metabolism. Lorenz and co-workers[15] produced hyperlipemia in immature fowl by injecting estrin, and they believe this has a direct effect upon lipid metabolism. The role played by the pituitary in lipid metabolism was investigated by Best and Campbell,[16] who injected anterior pituitary preparations into animals and produced a fall in body fat and an increase in liver fat. Houchin and Turner,[17] doing similar work in guinea pigs, produced a decrease in plasma fat and an increase in liver fat. Anterior pituitary preparations were administered by Holt and co-workers to a patient with idiopathic lipemia, and it was found that the blood fat was increased rather than decreased. Adrenalin has never been shown to play a definite role in lipid metabolism. Rony and Ching[18] administered adrenalin to dogs and found that it had no effect upon the blood. Jones and Fish[19] and Gildea and Man[20] injected epinephrine subcutaneously in

human subjects and were able to produce a moderate increase in the serum fatty acids, but the latter investigators doubt that adrenalin has any role in lipid metabolism.

There is more agreement concerning the pathologic conditions which may cause lipemia. These include:

1. Diabetes mellitus[6, 21, 22, 24, 25, 34]
2. Kidney disease, such as nephrosis and chronic glomerulonephritis[44-49]
3. Liver disease, as seen in obstructive jaundice and poisoning resulting from phosphorus, alcohol, carbon tetrachloride, chloroform, ether, and arsenic[7, 26-28]
4. Pancreatic disease[29]
5. Hypothyroidism[30, 31]
6. Starvation[6, 7]
7. Anemia, both acute and chronic, and purpura fulminans[6, 32, 33]
8. Von Gierke's disease[34-36]
9. Niemann-Pick disease[37, 57]
10. Occlusive vascular disease[38]
11. Dermatoses, psoriasis, and eczema.[4, 39] This is still open to discussion.
12. Idiopathic group[1, 3-5]

According to Gray,[21] Blix,[22] Joslin,[24] and Bloor,[6] lipemia is infrequent in mild diabetes mellitus. White and Hunt,[40] using cholesterol values as a measure of total lipids, found that hypercholesterolemia was rare in uncomplicated diabetes in children. In those cases with a tendency toward ketosis, there may be a high degree of lipemia. Jungbluth[41] and Marchbanks[42] have reported cases in males, 4 and 9 years old, who showed chemical evidence of diabetes mellitus, acidosis, and lipemia. Thompson and associates[43] collected seventeen such cases in adults who, in addition, presented xanthomatosis. In many of these cases, the lipemia and xanthomatosis responded to insulin and dietary therapy. Campbell[44] explains the lipemia of diabetes on the basis of a mobilization of fat from the body depots, since carbohydrate metabolism necessary for the production of energy is impaired.

Cases of von Gierke's diseases with lipemia have been reported by Hogg and Sidbury,[36] Krakower,[35] and Lindsay and co-workers.[34] Krakower stresses the disturbance in fat metabolism in addition to the faulty glycogen storage.

Lipemia has been found to occur in various blood dyscrasias, more commonly in the acute and chronic anemias. Boggs and Morris[33] and Horiuchi[32] were able to produce lipemia in dogs and rabbits by venesection. Bloor[6] and Horiuchi[32] feel that the anemia produces a temporary state of inanition which results in a mobilization of fat from the depots. The lipemia which is occasionally observed in severe cachexia or malnutrition may be ascribed to this mechanism.

Lichtenstein and Epstein[45] recently reported several cases of chronic glomerulonephritis and of lipoid, amyloid, and syphilitic nephroses in which lipemia was found. Other investigators have also demonstrated

an increase of total fatty acids, cholesterol, and phospholipids in nephrosis and the nephrotic stage of nephritis.[46, 47, 50] Page and Farr[46] showed that the lipemia of nephritis was not influenced by diet. Boyd[47] believes this persistent lipemia of nephritis is not alimentary in nature, but rather is a disturbance in plasma-tissue equilibrium due to kidney dysfunction. Shapiro[48] feels that the lipemia and cholesterolemia observed in nephrosis are not secondary to renal dysfunction, but that they are manifestations of disturbed lipoid-protein metabolism.

Bloch[52] suggests that the liver is the regulator of lipoid metabolism and that any disturbance in its function may cause lipoid imbalance. There are, according to Thannhauser and Magendantz,[26] two types of liver involvement with xanthomatosis. The first type is called xanthoma biliary cirrhosis and has no evident lipemia, although it may be masked. The second group is illustrated in a case described by Bürger and Grutz.[2] It is characterized by hepatosplenomegaly, lipemia, and xanthomata of the papular type. Montgomery,[27] in his review of cutaneous xanthoma with liver disease, associated mainly with obstructive jaundice, states that there may be a coexistent lipemia. Lipemia is also described in chloroform, arsenic, and alcohol poisonings; the action of these agents is chiefly on the liver.[4, 7] Chanutin and Ludewig[28] recently reported a case of disturbed lipid metabolism and xanthomatosis which they attributed to an arsenical hepatitis.

The pancreas, independent of its insulin production, is also believed to play a role in the metabolism of fat (Dragstedt and co-workers[12] and Entenman and associates[13]). Brunner[29] describes a case of acute pancreatitis with marked lipemia and quotes a similar case reported by Joel. With clinical improvement, the lipemia diminished. During the past few years, attempts have been made to correlate serum lipase values with pancreatic disease. Cherry and Crandall[51] found serum lipase present in only 6 of 146 routine dispensary patients, whereas Comfort and Osterberg[53] reported it constantly present in small amounts in patients without abdominal symptoms. It is agreed by the above investigators and by Baxter,[56] however, that elevated serum lipase values suggest the presence of pancreatic disease. Two determinations for serum lipase* in our patient showed its complete absence. Determinations of serum lipase in six normal children showed the presence of low serum lipase in four, and complete absence in two. No evaluation of the absence of serum lipase can be given, but Thannhauser[57] believes it may be a direct reflection of the activity of this enzyme in other organs of the body.

Hypothyroidism[31] is associated with high blood cholesterol values. Hurxthal and his co-workers studied numerous cases of myxedema and found cholesterolemia. Holt and his associates[4] administered thyroxin

*These lipase determinations were done by the laboratory staff of Dr. S. J. Thannhauser.

to their patient, and no effect upon the blood lipids was noted. We too treated our patient with thyroid extract and found no effect upon the blood lipid level.

Of the lipoidoses, only the Niemann-Pick disease[57] is due to an abnormal lipoid metabolism which may be associated with a marked lipemia. This disease presents a characteristic clinical picture. Despite the high phospholipid values of our patient, Niemann-Pick disease could be eliminated easily because of the clinical course.

Holt[4] was able to demonstrate a familial tendency of lipemia in his case. Examination of the bloods of the various members of our patient's family revealed no abnormal lipoid values. The following results were obtained: D. R., 291.0 mg. per cent fatty acids; P. R., 252.2 mg. per cent fatty acids; E. R., 352.00 mg. per cent fatty acids; R. R., 218.00 mg. per cent fatty acids; Mrs. R., 356.00 mg. per cent fatty acids; Mr. R., 400.00 mg. per cent fatty acids.

Opitz[1] and Franklin[3] reported cases in which the etiology of the lipemia could not be explained. A case of a 7-year-old boy with hyperlipemia, hepatosplenomegaly, and xanthoma was studied by Bernstein and his group.[5] Various metabolic studies, including respiratory quotients, failed to explain the mechanism of the lipemia, but it was observed that, on a low-fat diet, the blood lipids were lowered, that the liver and spleen decreased in size, and that the skin lesions cleared. Holt and his co-workers,[4] after conducting extensive hormonal and metabolic studies on an 11-year-old girl with extreme lipemia, hepatosplenomegaly, skin ulcerations, malnutrition, and bouts of abdominal pain, were also unable to ascribe any definite cause for the symptom complex. They likewise observed improvement in this patient while she was on a low fat diet; they suggest that the condition is due to a defective humoral mechanism for the removal of fat by the liver.

The relationship between xanthomatosis and lipemia has been amply reviewed by Thannhauser and Magendantz[26] and Montgomery and Osterberg.[27a] The former two feel that the skin manifestations are secondary to the hyperlipemia, as represented in the xanthomatoses of diabetes mellitus, and in those cases reported by Bürger and Grutz, and by Bernstein and associates. In the classification of xanthomatoses by Montgomery and Osterberg, they describe a group called juvenile xanthoma, characterized by a slightly elevated total fats level and flattened papular xanthomata. These lesions were found to involute when subjected to a low fat diet. The xanthomatous lesions in our case also cleared on a relatively low fat diet, but there was no recurrence when the patient was placed on a normal fat diet.

COMMENT

In an effort to determine the probable cause of the hyperlipemia, we carried out the following laboratory investigations:

Urines were yellow, acid, with specific gravity of from 1.010 to 1.020, no albumin, casts, or formed elements.

Examination of the blood revealed hemoglobin from 60 to 70 per cent (Sahli); red blood count, 3,500,000 to 4,300,000 per cubic millimeter; white blood count, 5,000 to 10,000 per cubic millimeter, with polymorphonuclear cells, 44 to 60; lymphocytes, 40 to 50, mononuclear cells, 3 to 4, and eosinophiles, 3 to 8. The red blood cells were normal in size, shape, and color. There were 179,000 platelets per cubic millimeter.

Stools were negative for guaiac and for pathogenic organisms. Fat and starch were present in normal amounts. The Hinton test was negative.

Fasting blood sugar levels were 85, 90, 70, and 100 mg./100 c.c. blood. The glucose tolerance test (2 Gm. glucose per kilogram) revealed 90 mg./100 c.c. blood at one-half hour; 129 mg./100 c.c. blood at one hour; 110 mg./100 c.c. blood at two hours; and 100 mg./100 c.c. blood at three hours.

Nonprotein nitrogen was 27 mg./100 c.c. blood; total protein, 6.5 Gm./100 c.c. blood; CO_2 combining power, 46 per cent; blood calcium, 9.8 mg./100 c.c. blood; blood phosphorus, 5.6 mg./100 c.c. blood; blood phosphatase, 2.75 Bodansky units; icteric index, 8; and blood amylase, 2.33 mg. maltose per cubic centimeter serum in one hour.

Blood enzymes: monobutyrin, 11 per cent splitting of 0.15 c.c. monobutyrin; tributyrin, 5 per cent splitting of 0.1 c.c. tributyrin; and lipase, 0 per cent splitting of 0.25 Gm. olive oil.

Variations in blood lipoids are tabulated in Table I.

Roentgenograms of the skull showed no abnormalities. The sella turcica was normal. The long bones revealed no pathological findings, and the epiphyseal centers were normal for the age of the child.

TABLE I*

	NORMAL VALUES	HOME DIET (MG. %)	LOW FAT DIET FOR ONE MONTH (MG. %)	LOW FAT DIET FOR TWO MONTHS (MG. %)	REGULAR HOSPITAL DIET FOR ONE WEEK (MG. %)
Total cholesterol	120-250 mg. %	379	330.0		
Free cholesterol	25-100 mg. %	158.5	114.7		
Cholesterol esters	100-200 mg. %	220.5	215.3		
Total phospholipids	100-350 mg. %	465	368.0		
Sphingomyelin	25- 40 mg. %	12.60	12.08		
Cephalin	75-150 mg. %	0.0	60.00		
Lecithin	75-150 mg. %	452.4	295.92		
Total fatty acids	500-800 mg. %	3115.0	1900.0	1311.0	2580.0

*The blood lipoid and enzyme determinations were done by the laboratory staff of Dr. S. J. Thannhauser.

Fluoroscopy with barium showed no abnormalities in the stomach or duodenum.

Lumbar puncture revealed normal dynamics, clear fluid, and no cells. The sugar and total protein were normal.

Table I illustrates the effect of a low fat diet upon the blood lipoids of this patient and gives a detailed analysis of the various constituents of the serum lipoids.

The above blood findings demonstrate that this patient with hepatosplenomegaly, normal phosphatase, absent jaundice, and elevated total cholesterol, but a normal ratio of free cholesterol to cholesterol esters, probably had no hepatic damage. It is noteworthy that on admission the sphingomyelin value was below normal and that no cephalin was found. After the patient had been on a low fat diet for one month, the cephalin was only slightly below normal and the sphingomyelin remained low. The lecithin, which was about three times above the normal value, was decreased on a low fat diet. This means that cephalin and sphingomyelin were probably not influenced by the diet, whereas lecithin values of the blood were directly influenced by the amount of fat in the diet. According to Table I, the increase of total fatty acids is almost entirely due to an increase of neutral fats.

We feel that our clinical and laboratory findings justify our classifying this case in the group of idiopathic lipemias.

SUMMARY

A case of a 1-year-old infant with lipemia, hepatosplenomegaly, lipemic retinalis, and xanthomatosis is presented. A detailed analysis of the serum lipids showed that the neutral fats were markedly elevated, whereas the phospholipids and total cholesterol were only slightly elevated. It was also found that no serum lipase was present. This is difficult to interpret, but it may suggest that in the organs concerned with fat metabolism the lipase values are low.

We are indebted to the laboratory staff of Dr. S. J. Thannhauser, Boston Dispensary, for the blood lipid determinations, and we gratefully acknowledge Dr. Thannhauser's many helpful criticisms.

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TETANY IN INFANCY AND CHILDHOOD

A Clinical Study of Forty-Five Cases Seen in North China With Especial Reference to Etiology

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THE present report is based upon the result of a study of forty-five cases of tetany which were seen in the pediatric service of the Peiping Union Medical College Hospital from January, 1921, to July, 1938. The criteria for the diagnosis of the disease were (1) hypocalcemia, with a serum calcium content of 8 mg. or less per 100 c.c., (2) typical attacks of spontaneous carpopedal spasm, and (3) other manifestations of tetany, such as convulsions, muscular spasms, Trousseau's sign, Chvostek's sign, or Erb's sign. For the inclusion of each case in this series, two of the three features enumerated above were required to be present. In thirty-nine cases it was possible to ascertain the serum calcium content before the institution of calcium therapy. In a few cases in which the determination of serum calcium was not made, spontaneous attacks of carpopedal spasms were observed. Special care was taken in the selection of our cases. A few patients with complications such as intracranial hemorrhage and meningitis were not included in the study, even though there were convulsions and somewhat low blood calcium values.

ETIOLOGICAL CONSIDERATIONS

Age Distribution.—In the Western literature infantile tetany is usually considered to be more frequently seen after the age of 6 months. According to the analysis of Guild,[1] the highest incidence of the disease was between the ages of 3 and 9 months. The age distribution of our series, however, is strikingly different. Thirty cases, or

Table I

Age Incidence of Patients With Tetany as Compared With That of Pediatric Patients in General

Age	Pediatric patients in general in 7½-month period in 1935-36		Patients with tetany	
	Number	Percentage	Number	Percentage
0- 3 mo.	159	9.1	30	66.7
3- 6 mo.	117	6.7	7	15.6
6-12 mo.	202	11.6	0	0.0
1- 2 yr.	301	17.3	2	4.5
2- 3 yr.	172	9.9	3	6.7
3- 5 yr.	269	15.4	1	2.0
5-12 yr.	525	30.0	2	4.5
Total	1,745	100.0	45	100.0

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TABLE II

THE DIET AND HEALTH CONDITION OF MOTHERS IN TWENTY CASES OF TETANY SEEN IN FIRST THREE MONTHS OF LIFE

HOSPITAL NUMBER OF INFANT	FEEDING	AGE AT ONSET OF SYMPTOMS OF TETANY	MOTHER'S CONDITION				ROENTGENOGRAM OF LONG BONES OF INFANTS
			DIET	EXPOSURE TO SUN	DISEASE	BLOOD CALCIUM X PHOSPHORUS	
47102	Breast feeding essentially	1st mo.	Adequate		Anorexia in last 2 months of pregnancy		Normal
53883*		2nd mo.	Low vitamin D		Osteomalacia	9 × 1.4 (during pregnancy)	Normal
54711*		2nd mo.	Low vitamin D		Osteomalacia		
54072		2nd mo.	Low calcium and vitamin D	Little	"Aching in legs"		Normal
54421		2nd mo.	Low calcium				Normal
54056		2nd mo.	(?) Low vitamin D	Little			
56005		2nd mo.	Low calcium				Normal
58396		2nd mo.	Low calcium and vitamin D	Little	Osteomalacia and tetany		Rickets
58528		2nd mo.	Low calcium and vitamin D	Little	Osteomalacia and tetany	7.3 × 3.0 (2 months after delivery)	Rickets
63009		2nd mo.	Low calcium and vitamin D				
54898		3rd mo.	(?) Low calcium and vitamin D				Rickets
40464	Artificial feeding essentially	1st mo.	Low vitamin D				Rickets
51045		1st mo.			"Low calcium" during pregnancy		Normal†
55550		1st mo.			Osteomalacia	8.6 × 2.7 (one week after delivery)	Normal
33489		2nd mo.	Adequate				Normal
33822		2nd mo.			Bacillary dysentery in last 3 months of pregnancy		Rickets
39949		2nd mo.			Osteomalacia	9.1 ×3.5 (two weeks after delivery)	Normal
60505		2nd mo.	Low vitamin D	Little	Osteomalacia	7.9 × 4.4 (day of delivery)	Rickets
60687		2nd mo.	Low vitamin D			9.2 × 2.3 (1½ months after delivery)	Rickets
61227		3rd mo.	Low vitamin D	Little	Osteomalacia		Rickets

*Same mother for these two infants.
†Mild rickets was demonstrated in the autopsy material.
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66.7 per cent, occurred before the age of 3 months; thirty-seven cases, or 82.2 per cent, before 6 months. As shown in Fig. 1, there were six cases in the first month of life and nineteen cases in the second month. From the third month on, the number of cases each month declined very rapidly.

The unusually high incidence of tetany in the first two months of life is decidedly a peculiar feature of the locality. Two possible explanations may be offered. First, it may happen that in our service we have a chance to see many more infants during the neonatal period than children at a later age. That such is not actually the case is well shown by the statistics compiled in Table I. The patients

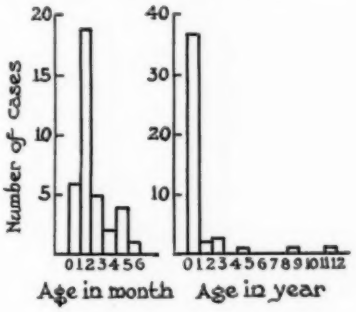

Fig. 1.—Age distribution.

below 3 months of age constitute only about 9 per cent of the total attendance of the clinic, while the incidence of tetany in the first 3 months of life is 66.7 per cent.

The second possibility is that there may be some local conditions with regard to the prenatal and postnatal care of the mother and the infant which would favor the development of tetany in the early months of life. An attempt was made to investigate the diet, mode of living, and general health of the mothers whose children had active tetany in early infancy. There were twenty cases in which such information was partially or completely available. The data are summarized in Table II. Among the twenty mothers, there were eight with a definite diagnosis of osteomalacia or tetany, six additional mothers with a history of diet grossly deficient in vitamin D or calcium or both, one who had had bacillary dysentery for three months just before delivery, and one who had had marked anorexia in the last two months of pregnancy. Thus, in sixteen cases, or 80 per cent, there was evidence of either definite or probable abnormality of calcium metabolism during the period of pregnancy and lactation. In this series, therefore, the lack of vitamin D and calcium in the mother seems to be essentially responsible for the development of tetany in the early months of infancy. The deficiency may exert its influence

upon the infant both in the fetal stage and during the early suckling period when the mother's milk is fed. This conception is consistent with the clinical investigation of Maxwell[2] that vitamin deficiency in the antenatal period may affect the fetus adversely. The experimental study of Sontag and his collaborators[3] in the rat also indicates that fetal mineralization is not independent of the mineral metabolism of the mother. Of considerable interest in this connection is the result of the recent metabolic study of Liu and his associates in this hospital.[4] They found that, when the infant of a mother with osteomalacia or tetany was fed exclusively on the mother's milk, the calcium balance was poor, and that, when the mother was given vitamin D, the infant who continued to be on the mother's milk showed a rapid improvement in the mineral metabolism and in the general clinical picture as well.

The occurrence of tetany in newborn infants was practically unknown in the older pediatric literature.[5, 6] In recent years, however, a number of reports have been made calling attention to the existence of this disease in the early weeks of life. Rothstein[7] aptly remarked, "The increasing frequency of reports of low calcium tetany in the newborn is obviously not due to an increased incidence of the syndrome but rather to increased watchfulness on the part of the physician and routine blood calcium determinations in cases of convulsions or twitches of unexplained etiology in the newborn." In 1937 Farr[8] gave a comprehensive review of the literature in a tabular form and reported three more cases of his own. The conditions in a country such as North China, where children are born and fed by mothers who frequently suffer from osteomalacia and severe grades of vitamin D deficiency, are fundamentally different from those seen in the Western part of the world. This may explain why in North China tetany is so frequent in infants below the age of 3 months.

Farr[8] and Bakwin[9] contended that hypoparathyroidism was an important factor in the pathogenesis of tetany in the neonatal period. We have not enough data to speak against this contention or in its favor. The fact that the value of serum inorganic phosphorus was extremely high in Case 2 is somewhat suggestive of such a possibility.

Coexistence of Rickets in Neonatal Period.—The data obtained in our neonatal cases are at variance with those of reported cases in the literature as far as the coexistence of rickets is concerned. The histories of the six patients seen in the first month of life (Cases 1 to 6) are to be presented in detail at the end of this paper. Their age at the time of onset of symptoms ranged from 12 to 28 days. The rachitic changes were demonstrated by autopsy in one patient (Case 4) and by x-ray examinations in three patients (Cases 3, 5, and 6). One infant (Case 2) was known to have been born of an osteomalacic mother during the active stage of the disease, although the roentgenograms of its long bones showed no rickets at the time of examination.

It is to be noted that in Case 3 the definite evidence of rickets was not found until a second roentgenologic examination of the long bones was made about one month after the onset of tetany, and that in Case 4 the post-mortem diagnosis of rickets was made one month after a negative result was obtained with the x-ray examination of the long bones. We believe that one negative x-ray examination at the time of diagnosis of tetany may not rule out an early stage of rickets, and that in such instances a balance study of calcium and phosphorus metabolism may be the only means of settling the problem.

Therefore, our material differs from the cases communicated in the Western literature in that the onset of tetany happens so often in the first three months, and in that our tetany patients often show rickets, even if they are no older than 3 months. It may be stressed again that both these differences must be explained by the fact that the mothers who bear and feed these patients suffer from abnormal vitamin D metabolism.

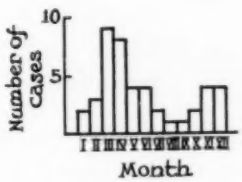

Fig. 2.—Seasonal incidence.

Seasonal Incidence.—The time of onset of symptoms was recorded in forty-four cases. As shown in Fig. 2, seventeen cases, or 38.6 per cent, occurred in the months of March and April. The lowest incidence was during the months of August and September. In Peiping, most of the infants and a number of mothers are confined indoors in the winter and early spring months, and they have little direct exposure to sunlight, so that by the end of spring, more cases of tetany are expected. In the present series none of the infants under 1 year of age received any direct sunlight, and only a few mothers had frequent exposure to the sun.

Birth History.—Out of forty cases with known birth history, seven patients, or 17 per cent, were born prematurely. It is generally believed that premature infants are liable to the development of tetany. The ages of these seven infants at the onset of tetany were all within the first 3 months, one case being in the first, four cases in the second, and two cases in the third month. This may suggest that there is a tendency for premature infants to develop tetany at an earlier age.

In thirty-nine cases the condition of birth was described as normal, easy, or spontaneous. No history of asphyxia, cyanosis, or bleeding

at the time of birth was recorded in any case. One patient was delivered by means of cesarean section. Birth injury as a possible cause of the presenting symptoms of convulsions is therefore unlikely.

TABLE III

DIET OF PATIENTS BEFORE THE DEVELOPMENT OF TETANY

DIET AT ONSET OF SYMPTOMS	NUMBER OF CASES IN FIRST 3 MONTHS OF LIFE	NUMBER OF CASES AFTER 3 MONTHS OF AGE	TOTAL CASES	PERCENTAGE
Breast fed exclusively	11	3	14	31.8
Breast fed, supplemented with carbohydrate or cow's milk	5	3	8	18.2
Cow's milk or its products shortly after birth				
Without added vitamin D	10	2	12	27.3
With concentrated vitamin D products	3	0	3	6.8
Mixed diet without addition of vitamin D products	0	7	7	15.9
Total number of available records	29	15	44	100

Dietary History.—Table III shows clearly that breast feeding is not an absolute safeguard against the development of tetany. Among all age groups, twenty-two patients, or 50 per cent, were fed with human milk, either exclusively or supplemented with a small amount of carbohydrate or of cow's milk. In twenty-nine cases under 3 months of age, there were sixteen, or 55.2 per cent, such cases. The conventional belief that tetany develops particularly in artificially fed infants[10] does not apply well for this series.

It is also very interesting to note that tetany developed in three infants who had been given a concentrated vitamin D preparation for periods of twelve, twenty, and twenty-eight days, respectively, preceding the onset of the disease.

Correlation of Roentgenologic, Chemical, and Clinical Signs of Rickets.—X-ray examinations of the long bones were made shortly after admission in thirty-six cases. For this group, the roentgenologic, clinical, and chemical findings pertaining to rickets are correlated in Table IV. Roentgenologically, ten cases, or 27.8 per cent, showed no evidence of rickets, fourteen cases, or 38.9 per cent, mild rickets, and twelve cases, or 33.3 per cent, moderate or severe rickets. Thus, the majority of the patients, or 72.2 per cent, had some x-ray evidence of rickets. In Table III, it may be seen that the younger the patient with tetany, the less likely is the roentgenologic finding of rickets. The only patient in the age group older than 3 months whose roentgenograms showed no changes other than general osteoporosis was a child whose tetany related to chronic nephritis. Healing rickets was described only twice, once in a severe case and once in a mild case.

TABLE IV

CORRELATION OF THE ROENTGENOLOGIC, CLINICAL, AND CHEMICAL FINDINGS PERTAINING TO RICKETS IN THIRTY-SIX CASES

	AGE	NUMBER OF AVAILABLE RECORDS	CASES WITH SEVERE AND MODERATE RICKETS	CASES WITH MILD RICKETS	CASES WITH NO RICKETS
Roentgenologic signs	1 mo.	6	1	2	3*
	2 mo.	14	1	7	6
	3 mo.	5	2	3	0
	4 mo.	11	8	2	1†
	Total	36	12	14	10
Clinical signs	1 mo.	6	0	1	5
	2 mo.	13	1	4	8
	3 mo.	5	2	3	0
	4 mo.	11	8	2	1
	Total	35	11	10	14
Product of serum calcium and inorganic phosphorus determined before treatment‡	1 mo.	5	36	31, 49	46, 75
	2 mo.	8	29	27, 34, 40, 42, 55 62	43
	3 mo.	4	31	28, 35, 42	0
	4 mo.	11	9, 10, 10, 26 26, 31, 35, 38	34, 43	35
	Total	28	11	13	4

*One of the three cases was shown to have rickets at autopsy one month later.
†General osteoporosis (in a case of chronic nephritis).
‡The values of the Ca x P product in the table are grouped according to the roentgenologic signs.

Clinically, twenty-one of thirty-five patients, or 60 per cent, showed rachitic signs of varying degrees, mostly moderate and mild. In regard to the product of serum calcium and inorganic phosphorus, it was below 35 for nine of the eleven cases showing x-ray evidence of moderate or severe rickets, but higher figures were obtained in cases with mild, or no, rickets. For the group of patients under 2 months of age who showed no visible rachitic changes in roentgenograms, the serum phosphorus, and hence the product, was usually higher than normal, the latter occasionally going as high as 75. We believe that such a finding in the early weeks of life does not necessarily rule out the possibility of an incipient rachitic process. A high value of serum inorganic phosphate has been known to coexist with rickets not uncommonly in the early months of life in premature infants.[11] If such very young patients were left untreated and repeatedly followed up, there might be more chance of observing evidence of rickets in the roentgenograms. Taking all the available evidence of this series, one may say that rickets was present in a great majority of patients with tetany, and that most of these patients showed clinical and laboratory signs of mild, rather than severe, rickets.

Association With Other Diseases.—Acute febrile infections have been generally recognized to precipitate the active symptoms of the disease where only a latent tetany previously existed. In this series, acute upper respiratory infections were found to precede tetany in four

cases, otitis media in three cases, subcutaneous abscesses in one case, and pyelitis in one case. Gastrointestinal disturbances may play an important role through the poor absorption of calcium and vitamin D from the food. In four cases there was diarrhea just preceding the onset of tetany. In one patient there was a protracted course of jaundice for more than three months. Whether or not there was a lack of secretion of bile from the immature liver leading to a deficient assimilation of vitamin D[12, 13] is difficult to ascertain.

Impairment of Renal Function.—A low level of blood calcium may be caused occasionally by hyperphosphatemia, which in turn is the result of retention of phosphate due to the impairment of the renal function. This explains the tetany of nephritis in one of our cases, the detailed history of which was reported by Fan and Chin.[14]

SYMPTOMS AND SIGNS

Symptoms.—The most frequent and alarming symptoms of the disease were convulsions, which were present in thirty-five cases, or 77.7 per cent. As pointed out previously,[1, 15, 16] the convulsions may be the only manifestation of the increased excitability of the neuromuscular system, particularly in the case of younger infants. They were repeated in thirty-one of the thirty-five patients and occurred in a single attack in the other four cases. They occurred once in from one to two days or as frequently as from ten to twenty times in one day. Each attack lasted from a few seconds to about one-half hour. The convulsive seizures were usually generalized and clonic, and they involved chiefly the muscles of the extremities, face, and eyes. At times, the twitching movements were confined to one side of the body as described before by Powers.[15] In most instances they were bilateral, but one side might be more involved than the other. The rolling up of eyeballs, the retraction of the head, and the appearance of foam at the mouth were frequently observed. Incontinence of urine and feces was seen in a few instances. Consciousness was usually lost during the convulsions, but in most of the cases it returned shortly after the attack was over.

We are aware of the comment of Birk[17] and others that convulsions in early infancy are nearly always due to pathologic processes in the brain. This may be so in the Western part of the world, where, evidently, too many convulsive states during infancy are erroneously labeled as infantile tetany. However, the evidence gathered in this study indicates that in Peiping an intimate relationship exists between the convulsions seen in the first few months of life and the disturbance of calcium and vitamin D metabolism. The frequency of osteomalacia in the mothers of our patients, the typical seasonal incidence of this series, and the improvement of the mineral metabolism of the sucklings after they had been fed on breast milk from mothers

receiving vitamin D, as shown by Liu and his associates—all are in agreement with the diagnosis of infantile tetany, even though one may doubt the pathognomonic significance of hypocalcemia in this disease.

Carpopedal spasm, one of the well-known characteristic features of the disease, was seen in only thirteen cases, or 29 per cent, of the present series. Among patients below 6 months of age, it was noticed in but four cases. It was found in association with active convulsions in four cases and without accompanying convulsions in nine cases. When there were generalized convulsions, the fingers were usually clenched together rather than extended. The preponderance of convulsions over carpopedal spasms was apparently related to the large number of infants in this series. Laryngospasm was seen in only one instance. The abnormalities which were sometimes complained of by the parents or other informants were low-grade fever, running of nose or ears, mild cough, diarrhea, cyanosis, slight dyspnea, and vomiting. The appetite only rarely failed, unless there were coexisting infections.

Physical Findings.—A normal temperature is usually found in an uncomplicated case of tetany. Of course, when the disease is complicated with infections, fever may be observed. In our series, the highest temperature ever attained was 42° C. in a patient ill with pneumonia who died eight hours after admission. There was one patient with latent tetany with a subnormal temperature below 35° C. Chvostek's sign was present in thirty-one cases, or 66.6 per cent, being best elicited during the intervals between the successive convulsive seizures. Three of the thirty-one cases were seen during the first month of life. Following treatment, it usually disappeared a few days after the convulsions or spasms were gone. That this sign is of no diagnostic significance during the neonatal period has been repeatedly confirmed. Von Reuss[6] stated, "The facial phenomenon, contraction of the muscles of the face on tapping the hinder portions of the cheek, occurs frequently in newborn infants." Stevenson, Mitchell, and Koch[18] found that, in normal newborn infants from 12 hours to 21 days old, a Chvostek sign occurred consistently without blood chemical or electric evidences of tetany. Trousseau's sign, or the artificially produced carpopedal spasm, occurred in ten, or 22 per cent, of our cases. During active convulsive seizures, some degree of fullness or even a little bulging of the anterior fontanel may be observed. But a persistent fullness of the fontanel in the intervals between convulsions should suggest an organic disease of the central nervous system. A lumbar puncture is then indicated.

Calcium and Phosphorus Contents in the Blood.—In this series, determinations of serum calcium and inorganic phosphorus* were

*These determinations were made in the chemical laboratory of the Department of Medicine, Peiping Union Medical College.

made before the institution of calcium therapy in thirty-nine and thirty-five cases, respectively. In the analysis for calcium, the method of Kramer and Tisdall as modified by Clark and Collip[19] was used; for the determination of inorganic phosphorus, the procedure of Fiske and Subbarow[20] was followed. The results are shown in Fig. 3.

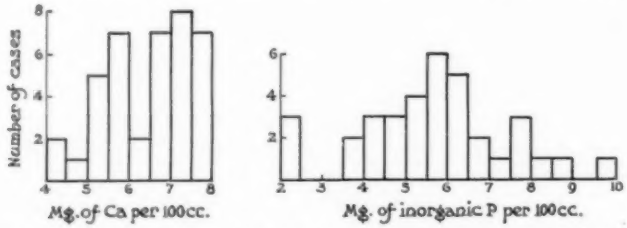

Fig. 3.—Values of serum calcium and inorganic phosphorus before treatment.

Of the group of thirty-nine patients with the record available of serum calcium just before the treatment, thirty-five cases, or 85 per cent, showed a calcium concentration of between 5 and 8 mg. per cent. There was no parallelism between the level of serum calcium and the severity of symptoms. The serum inorganic phosphorus was high, normal, or low, ranging from 1.9 to 10.0 mg. per cent. In seven cases, or 20 per cent, the values were above 7 mg. per cent. All of the seven cases occurred in patients under 3 months of age, two in the first month, four in the second month, and one in the third month. Only one of the seven infants was born prematurely. X-ray examinations of the long bones were made in six cases, and mild rickets was reported in three of them. The active symptoms of tetany responded very well to calcium treatment in all the patients with high phosphorus concentrations. The result of our clinical study of these seven cases tends to confirm the impression of Marples and Crump[21] that the group with high concentrations of serum phosphorus could not be differentiated on clinical grounds from those with normal or low phosphorus values.

Recently, McLean and Hastings[22] proposed that the total calcium of the serum is nearly all accounted for by calcium ions and calcium bond to protein and that the ionized calcium, which is of primary physiologic and clinical importance, may be calculated from the total calcium and total protein by a mass law equation. In nineteen cases of our series, the total serum protein was determined simultaneously with serum calcium and inorganic phosphorus. The values of ionized calcium thus calculated were all found to be less than 4.25 mg. per cent, the lower limit of the normal, according to McLean and Hastings. In practice, therefore, it is desirable to determine serum protein for the calculation of calcium ions only when the total calcium value is above 8 mg. per cent.

Other Laboratory Findings.—There was nothing unusual about the hematologic data. Lumbar punctures were done in twenty cases. In sixteen cases the spinal fluid was normal. In three cases it was bloody, apparently due to a local trauma. In only one patient were there definite findings of increased protein and cells, and this was because he was suffering from congenital syphilis as well as tetany.

TREATMENT

Symptomatic Treatment.—It is imperative to stop active convulsions by some emergency measure, such as ether inhalation, rectal administration of chloral hydrate, or hypodermic injection of morphine. Since the underlying cause is the lowering of serum calcium, the convulsive seizure may return as soon as the temporary effect of the sedatives is over.

Calcium Therapy.—The oral administration of calcium chloride was depended upon almost exclusively to correct the calcium deficiency. Not only does it directly supply the calcium ion, but also, by virtue of its acid-producing property, it increases the ionization of the calcium already present in the serum. When a sufficient amount of the drug is instituted, it usually stops the recurrence of convulsions within a few hours. In our practice, as soon as the active convulsions of tetany are under control, an initial dose of from 2 to 4 Gm. of calcium chloride is given in the form of from 20 to 40 c.c. of 10 per cent solution by mouth, and gavage is resorted to if necessary. This is then followed by a daily maintenance dose of from 2 to 4 Gm. of the salt, giving from 5 to 10 c.c. of 10 per cent solution every six hours. This does has to be maintained for from ten to fifteen days. We feel that such a scheme, supplemented by the use of a potent vitamin D preparation, is sufficient to ensure a permanent cure. Doses smaller or duration of treatment shorter than suggested here may bring forth a temporary cure, but relapse of symptoms is not uncommon.

On the other hand, a liberal amount of calcium chloride should be given only under careful supervision in order to avoid the risk of acidosis. L. H. C. (Case 4) had persistent diarrhea prior to the onset of acidosis. Another patient had signs of an acute respiratory infection when the acidotic type of breathing made its appearance. Still another had high fever during the greatest part of the hospitalization period. The doses of calcium chloride given could not be criticized as excessive. Yet, a clinical picture of marked acidosis, confirmed by the study of the alkali reserve of the blood, was observed during the course of the treatment. Presumably, the acid affect of calcium chloride plays a role in aggravating the already existing tendency to acidosis due to febrile or diarrheal diseases. In our minds, calcium chloride is a potent drug and should be administered

with due precaution, especially when a respiratory infection or a gastrointestinal disturbance is coexistent. In treating dispensary patients with liberal doses of this drug, one must not prescribe a large quantity of it at one time. The patients should be asked to return every two or three days for follow-up examinations and renewal of the prescription. This should be particularly emphasized in cases with complicating diseases such as acute respiratory infections, diarrhea, and renal insufficiency.

The Swiss preparation of 10 per cent solution of calcium gluconate (Sandoz) has been given frequently intramuscularly or intravenously. The dose is from 5 to 10 c.c., which may be repeated several times a day. The advantages of this preparation are twofold—the possibility of its administration even during the active stage of convulsions, and the more immediate effect, particularly in the case of intravenous therapy. Its drawbacks are the relatively high cost and the possibility of producing local or remote deposits of calcium salts in the body, as recently described by Shannon.[23]

Other Treatment.—Calcium therapy alone may elevate the serum calcium temporarily, but it cannot effect a cure. The active symptoms of tetany will recur until vitamin D is supplied in sufficient amount, either in the form of liver oils, irradiated ergosterol, or irradiated food, or by directly exposing the patient to the ultraviolet rays. It is necessary, therefore, to start antirachitic treatment simultaneously with, or a few days after, the commencement of calcium therapy. In order to bring the serum calcium to a normal level within a short period, concentrated preparations of vitamin D are preferable. Besides the use of vitamin D preparations, dihydrotachysterol (A T_{10}) has been considered promising in certain cases of tetany in infancy, namely, those cases in which there is a very high value of serum phosphorus and in which parathyroid deficiency may play a role in the pathogenesis of the disease.[23] However, in our cases, which, we feel, are most frequently associated with vitamin D deficiency, it is doubtful if the new preparation will have any therapeutic advantage.

PROGNOSIS

Uncomplicated cases of tetany, if correctly diagnosed and appropriately treated, have an excellent prognosis. In the presence of severe infection, however, the disease may be resistant to the treatment which is ordinarily effective. The case fatality of this series was 20 per cent. The chief causes of death were various infections in six cases, neoplasm of the liver in one case, "idiopathic hypertrophy of the heart" in one case, and probably laryngospasm in another case. Except for the latter case, none of the deaths were directly related to the disease of tetany.

SUMMARY AND CONCLUSIONS

Forty-five cases of tetany seen in the pediatric service of the Peiping Union Medical College Hospital were studied with especial reference to the etiologic factors.

We are well aware that some clinicians are of the opinion that spasmophilia of early infancy as described in the Western part of the world is not to be compared with tetany of adults. We, however, hold that our cases represent the real type of infantile tetany, that is, a disease purely due to hyperexcitability of the peripheral neuromuscular apparatus because of a decrease in calcium or calcium ions circulating in the peripheral blood. As a matter of fact, our material differs from the cases found in Western literature because (a) many of our cases occurred in the first three months of life, (b) 80 per cent of the mothers of our patients showed an impaired calcium metabolism during pregnancy and lactation, and (c) many of our patients showed rickets during the first three months after birth. All three of these factors are related. They prove that congenital lack of vitamin D and calcium is evidently an important factor in the pathogenesis and the clinical characteristics of infantile tetany as seen in Peiping.

The association of tetany with rickets was carefully analyzed in the whole series. In 72.2 per cent of the cases, there was visible roentgenologic evidence of rickets, most of which was mild. The younger the patient, the less likely was the finding of rachitic changes in the x-ray films. In one patient, whose onset of tetany was at the age of 23 days, no evidence of rickets was found until a second roentgenologic examination of the long bones was made about one month later. In another case, a post-mortem diagnosis of rickets was made one month after a negative result was obtained with the x-ray examination of the long bones at the onset of tetany when the patient was 25 days old. Such instances indicate that one negative x-ray examination at the time of diagnosis of tetany may not rule out the possibility of an incipient rachitic process.

In 50 per cent of the cases, the patients were breast fed before the development of tetany. In a community where mother's nutrition is not well taken care of, human milk should not be relied upon to protect the sucklings from tetany.

Gastrointestinal disturbances may play an important part in the production of tetany. In the presence of persistent diarrhea even the administration of concentrated preparation of vitamin D for several weeks failed to prevent the appearance of tetany.

REPORT OF CASES

CASE 1.—P. W. Y. (Hospital No. 47102), a Chinese male infant, was admitted to the hospital on Nov. 14, 1934, the day of birth, because his mother was hospitalized for retention of the placenta. The course of the mother's gestation was

said to have been smooth until the last two months, when she complained of marked loss of appetite and general malaise. Her diet was considered to be adequate during the period of pregnancy. Eggs, meat, and fresh vegetables were taken frequently. The infant was born spontaneously at full term. Physical examinations on admission showed normal findings. Breast feeding was started on the second day of life, and evaporated milk was started for complementary feedings on the seventh day.

On Nov. 25, 1934, the twelfth day of life, there were about seven convulsive seizures, and there were five more attacks on the next day. The convulsions consisted of clonic contractions of the extremities and twitching of the facial muscles, each attack lasting for a few minutes. Chvostek's and Trousseau's signs were negative. There was no clinical evidence of rickets. An x-ray examination of the long bones showed "visualized bones normal in contour, size, and density." Serum calcium was 7.9 mg. per cent (Nov. 26). The blood Kline test was negative. The temperature was normal.

Doses of calcium chloride in 10 per cent solution were begun on Nov. 26, with an initial dose of 15 c.c., followed by 10 c.c. every four hours. Haliverol (Parke, Davis), 0.1 c.c. daily, was begun on Nov. 25. No more convulsions occurred after Nov. 26. The patient was discharged in good condition on Nov. 28, and it was advised that he continue the calcium chloride at home for one more week.

CASE 2.—Y. S. C. (Hospital No. 55550), a Chinese female infant, was delivered by cesarean section on Aug. 20, 1936, on account of osteomalacia in the mother, whose serum calcium was 8.6 mg. per 100 c.c. and whose serum inorganic phosphorus was 2.7 mg. per 100 c.c. one week after the child was born. The birth weight was 3,040 Gm. The infant had been fed with a formula consisting of klim and cane sugar since the third day of life. No extra supply of vitamin D was given. Feedings were well taken, and there was no diarrhea or febrile disease. On Sept. 5, 1936, the seventeenth day of life, the patient began to have repeated attacks of muscular twitchings of the face, unaccompanied by generalized convulsions, cyanosis, or respiratory difficulty. Chvostek's sign was positive bilaterally. There was no sign of rickets either clinically or roentgenologically. The x-ray examination of the long bones had been made on Aug. 24, 1936. It was not repeated afterward. Serum calcium was 7.5 mg. per cent, and phosphorus, 10 mg. per cent.

Treatment consisted of the administration of calcium gluconate (5 c.c. of 10 per cent solution intramuscularly twice on Sept. 5) and repeated doses of calcium chloride by mouth (10 per cent solution, 5 c.c. three times a day on Sept. 5, to 6.4 c.c. twice a day from Sept. 6 to 11, followed by 2 c.c. twice a day for one more week at home). Haliverol (Parke, Davis) was administered in a dosage of 6 drops daily from Sept. 5 to 11, and cod-liver oil, 12 c.c. daily, beginning Sept. 11. The twitching of the facial muscles stopped soon after the commencement of the treatment. On Sept. 11 the serum calcium was 8.6 mg. per cent, and the phosphorus, 7.2 mg. per cent. There was no recurrence of symptoms up to Sept. 17, when the baby was last seen.

CASE 3.—T. T. Y. (Hospital No. 36217), a Chinese male infant, was born spontaneously at full term in the hospital on June 6, 1932, with a birthweight of 2,250 Gm. The cord blood calcium was 11 mg. per cent. He was breast fed. After being sent home on June 15, he was perfectly well until June 29, when he began to have attacks of twitching of the corners of the mouth and rhythmic movements of the extremities. Each attack lasted for from one to five minutes. There was no loss of consciousness. The attacks became more severe on July 6, with cyanosis, dyspnea, and rolling up of the eyeballs. However, the baby appeared perfectly normal during the intervals between the successive attacks. At the time of ad-

mission on July 7, the patient was found to be conscious and to have prominent parietal bosses. Trousseau's and Chvostek's signs were negative. An x-ray examination of the long bones showed slight generalized osteoporosis, but no evidence of rickets. Serum calcium was 7.8 mg. per cent, and phosphorus, 4.2 mg. per cent. A study of spinal fluid showed normal findings, including a negative Wassermann reaction.

On July 7 and 8, the patient was given 4 c.c. of a 10 per cent solution of calcium chloride every four hours, and 4 c.c. of a chloral hydrate mixture twice a day. No more convulsions were observed, and the patient was discharged home on July 13, 1932, without advice of further medication. Beginning on July 19, repeated attacks of generalized convulsions were observed, and the infant was readmitted on July 24. This time Chvostek's sign was positive. Serum calcium was 5.6 mg. per cent, and phosphorus was 6.4 per cent. Calcium chloride therapy was resumed immediately after admission, but the convulsions kept recurring until July 28. On Aug. 4, another x-ray examination revealed cupping and irregularity involving the diaphyseal ends of the long bones, particularly evident at both wrists and ankles. Very extensive periosteal changes were also observed. The impression of the roentgenologists was "rickets, moderate and active." No vitamin D was added to the diet before Aug. 4. Since then a liberal amount of vitamin D substances was administered, and follow-up roentgenologic examinations of the long bones showed progressive healing rickets.

CASE 4.—L. H. C. (Hospital No. 51045), a 15-day-old Chinese male infant, was admitted on Oct. 10, 1935, for mild diarrhea since the fourth day of life. He had been fed artificially without satisfactory results. Birth was normal at full term. During the late part of pregnancy, the mother was told by her attending obstetrician that her blood calcium was subnormal, and consequently she received some medicinal preparations containing calcium. On admission, the infant was dehydrated and weighed 2,730 Gm. A systolic murmur was audible over the whole precordium, being loudest at the apical region. There was a persistent low-grade fever. Stools were loose, occurred about ten times a day, and occasionally showed blood cells on microscopic examination. Stool cultures were negative. The blood Wassermann reaction was negative. The dehydration was combated by parenteral administration of fluids. Evaporated milk and dextrimaltose mixtures were given in increasing amounts. Haliverol (Parke, Davis), 0.2 c.c., was administered once or twice daily every day since admission.

Between 1:30 A.M. Oct. 20 and 7:30 A.M. Oct. 21, 1935, the patient had thirty-eight attacks of generalized convulsions, each attack lasting for one or two minutes. Chvostek's sign was positive. Serum calcium was 7.4 and phosphorus 6.2 mg. per cent. Roentgenograms of the long bones showed normal findings. The convulsions were soon controlled by means of calcium gluconate (6 c.c. of 10 per cent solution intramuscularly the night of Oct. 20) and calcium chloride (1 Gm. daily on Oct. 20 and 21, and 3 Gm. on Oct. 22, 23, and 24).

On Nov. 7, his stools became more watery, and the temperature mounted a little. Convulsions recurred on Nov. 15. Five cubic centimeters of 10 per cent solution of calcium gluconate were injected intramuscularly four times on Nov. 16, and calcium chloride was given orally in doses of 3 Gm. a day from Nov. 16 to 20. There were no more attacks after Nov. 17.

Toward the evening of Nov. 20, the patient developed a fever of 39° C. and an acidotic type of breathing, followed by severe diarrhea and a clinical picture of marked dehydration. He died the next day.

At autopsy, the positive findings were mild rickets, interventricular septal defect, hypertrophy of the right ventricle, early acute colitis, and dilatation of the left ureter. Microscopically, the costochondral junctions showed from slight to moderate swelling. The line of ossification of the ribs was irregular.

CASE 5.—C. Y. S. (Hospital No. 36291), a Chinese male infant, was delivered normally at full term and was fed on his mother's milk at irregular intervals. Beginning on the twenty-eighth day of life, transient convulsive attacks with stiff extremities occurred almost daily. He was admitted to the hospital on June 13, 1932, the seventy-seventh day of life, with the story that convulsions had become more frequent in the previous week and that they were accompanied at times by difficulty of breathing. Physical examination showed a dehydrated and undernourished baby, with positive findings of craniotabes, rosary, and enlarged wrists. His temperature ranged between 38 and 40° C. Serum calcium was 7.5 mg. per cent, and phosphorus, 6.5 mg. per cent. The blood Wassermann reaction was negative. The spinal fluid was normal, including a negative Wassermann reaction. Roentgenograms of the long bones taken on June 14 indicated a mild degree of rickets. The epiphyseal ends of the radii and ulnae at both wrists showed definite marginal sharpening and tendency of cupping. A marked periosteal change was noted along the shaft of the right ulna, both femora, tibiae, and fibulae. The bony trabeculations of the long bones were coarse.

Since admission, the patient was fed with lactic acid klim plus cane sugar. Calcium therapy was started on June 14, 4 c.c. of 10 per cent calcium chloride being administered orally every four hours up to July 3. Vigantol was given in doses of 10 drops daily from June 13 to 20, and 15 drops daily from June 20 to July 12. Twelve cubic centimeters of cod-liver oil were given daily beginning July 12. Convulsions became less frequent, and after June 18 there were no more seizures. The serum calcium was 7.7 mg. per cent on June 17, and 9.7 mg. per cent on July 18. When the x-ray examination was repeated on July 9, it was noted that the diaphyseal ends of both radii and ulnae appeared denser and more regular, showing improvement of the rachitic changes.

The serum calcium and phosphorus of the mother, determined on June 17, were 10.9 and 3.7 mg. per cent, respectively. The Wassermann reaction and the Kahn test of the mother's blood, taken on June 22, were both negative.

CASE 6.—W. S. M. (Hospital No. 40464), a 32-day-old Chinese female baby, was admitted to the hospital on May 30, 1933, with the history of one attack of mild and transient clonic convulsions on May 26, followed by similar attacks on May 29 and 30. The baby was delivered normally at full term and was weaned at the age of 13 days. Evaporated milk formula had been given since.

On admission, the patient's weight was 2,700 Gm. The temperature was normal. There was no clinical sign of rickets, but the x-ray examination of the long bones (June 1, 1933) showed definite evidence of mild rickets with tendency of healing. There was a general osteoporosis of the visualized long bones, more marked for the radii and ulnae. Bony trabeculations near the epiphyseal ends were coarser than usual. The epiphyseal ends of the diaphyses showed mild, but definite, irregularity and also some degree of bony condensation. Cupping deformity was observed at the distal ends of the ulnae, tibiae, and fibulae. Serum calcium was 6.8 and phosphorus 4.5 mg. per cent. The blood Wassermann and Kline tests were negative. Spinal fluid was entirely normal. On May 31, Trousseau's sign was found to be positive. Calcium therapy was started on the second day of admission (4 Gm. of calcium chloride daily from May 31 to June 5, 3.2 Gm. daily from June 5 to June 9, and 1.2 Gm. daily from June 9 to June 12). Haliverol (Parke, Davis) and cod-liver oil were administered beginning June 5, and the patient was exposed to direct sunlight beginning June 7. No convulsions had been observed since admission. On June 6 Trousseau's sign was no longer obtainable, and the serum calcium and phosphorus were 9.1 and 4.7 mg. per cent, respectively.

We wish to express our thanks to Professor Isidore Snapper for the valuable suggestions which he offered during the preparation of the paper.

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CAPILLARY FRAGILITY AND ASCORBIC ACID STUDIES

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Göthlin,[1] in 1933, stated that capillary strength determined by his method of testing revealed indirectly the vitamin C content of the body. His conclusion was confirmed by Wright[2] who employed a modification of the Rumpel-Leede capillary fragility test.

Beginning in September, 1936, we performed vitamin C determinations in the blood plasma on a group of children admitted to the Pediatric Service of Mount Sinai Hospital. Some of these children showed a normal capillary fragility test with subnormal levels of vitamin C in the blood plasma, while others showed the reverse phenomenon. Because our preliminary findings were in disagreement with those recorded by the above-mentioned investigators, we decided to study the question by making studies on a larger group of children. The present study comprises 150 children, ranging in age from 5 to 13 years, 41 of whom had some stigmas of rheumatic disease.

MATERIAL AND METHODS

About 3 c.c. of blood was withdrawn from the antecubital vein of a fasting child and placed in a test tube containing a small amount of potassium oxalate. The tube was rotated gently so that the blood would become properly oxalated. The Farmer-Abt modification of the Tillmans-Hirsch titration method was used for the determination of the amount of reduced vitamin C in 100 c.c. of blood plasma, and the result was recorded in milligrams per cent. The dye substance of 2.6 dichlorendophenol was used for the titration. We accepted from 0.7 mg. to 2.0 mg. per cent vitamin C content of the blood plasma as normal and below 0.7 mg. per cent as a subnormal level. The dye substance used in our titration was either made up freshly every seven days or restandardized at this interval. The 5 per cent metaphosphoric acid was likewise freshly prepared every seven days. In performing the test for capillary fragility, we employed the modification of the Rumpel-Leede test as suggested by Wright.[2] The blood pressure cuff was applied above the elbow, and the blood pressure was raised to a level halfway between systolic and diastolic and maintained at this level for fifteen minutes. The cuff was then removed. Five minutes later the average number of petechiae appearing in each of two horizontal circles located about 4 cm. below the antecubital fossa were counted. The diameter of each circle was about 2.5 cm. These deter-

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minations were done immediately after blood was withdrawn for the estimation of vitamin C content. We accepted Wright's standard of ten or less petechiae as normal, from ten to twenty as borderline, and twenty or more as evidence of capillary fragility.

RESULTS

The figures obtained in our series of cases may be conveniently classified as follows:

1. Sixty children, or 40 per cent of the series, were found to have a normal ascorbic acid level in the blood plasma, along with a normal capillary fragility test.

2. Thirty-two children, or 21.3 per cent, showed a normal level of ascorbic acid in the blood plasma, with a positive or abnormal capillary fragility test.

3. Forty-one children, or 27.3 per cent, showed a subnormal level of ascorbic acid in the blood plasma, with a normal capillary fragility test.

4. Seventeen children, or 11.3 per cent, showed subnormal figures for the ascorbic acid content of the blood plasma, with a positive capillary fragility test.

The determinations show parallelism in 51 per cent of the cases, whereas in 49 per cent of the cases a discrepancy exists between the capillary fragility test and the plasma ascorbic acid level.

These findings clearly indicate that an abnormal (positive) capillary fragility test does not necessarily denote a state of avitaminosis C, nor does a normal capillary fragility test signify adequacy of the vitamin C content in the blood. Greene[3] was among the first to point out that a positive reaction to a capillary resistance test does not necessarily denote avitaminosis C, a conclusion later confirmed by Perry.[4] Abt and his co-workers,[5] in a study of vitamin C in the blood plasma and the capillary fragility test in a group of children who were placed on diets adequate in vitamin C, concluded there was no uniform or constant agreement between the two tests mentioned. Liebman and associates,[6] using both the Wright modification of the Rumpel-Leede test and Dalldorf's suction cup method, found little agreement between blood plasma vitamin C and either of the tourniquet tests.

The causes for excessive capillary fragility are many, among which may be mentioned the following which are well known: thrombocytopenic purpura, hemophilia, neoarsphenamine and other drugs, anaphylactoid purpura, acute nephritis, toxins, e.g., diphtheria, scarlet fever, acute infections, menstruation, and anemia. Since the vitamin C factor cannot be associated in some manner with excessive capillary fragility, it is possible that some other vitamin factor may be involved. We suspect the new vitamin substance discovered by Szent-Györgyi,

vitamin P, may be the main factor responsible for the maintenance of the normal capillary wall. Studies along these lines are now being undertaken.

SUMMARY

A study was conducted on a group of 150 children in whom titrations of vitamin C content in the blood plasma, along with capillary fragility tests, were made. There appeared to be no correlation between abnormal capillary fragility tests and avitaminosis C.

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VALUE OF THE TUBERCULIN PATCH TEST IN CASE FINDING

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CASE finding means the discovery of cases with tuberculous lesions not yet arrested, rather than the finding of positive reactors to tuberculin. The question to be answered in this paper is, therefore, whether or not children with active tuberculous lesions are missed by the tuberculin patch test (Vollmer-Lederle).[1] This study comprises three groups of children, totalling 2,000 cases.

Group 1 consisted of 847 children admitted to the Mount Sinai Hospital and was similar to the average group of children admitted to a pediatric department for various conditions and careful study. Presence or absence of tuberculosis was investigated in every case with tuberculin tests and physical examination, and by roentgenographic examination in the majority of the cases. Search for tubercle bacilli in sputum or gastric lavage usually followed in contact cases or whenever there was reasonable suspicion of a tuberculous infection despite negative tuberculin tests or x-ray findings of the chest.

The tuberculin tests were carefully applied, and there were repeated opportunities for reading and following the reactions. Even unusually late reactions did not escape observation. The reactions were read by the interns and residents, not by the author, who was consulted only rarely in doubtful cases. Table I shows the results.

TABLE I

CASES (847)	PATCH TEST	MANTOUX TEST		CLINICAL, ROENTGENOGRAPHIC, OR BACTERIOLOGIC FINDINGS SUGGESTIVE OF TUBERCULOUS INFECTION
		1.0 MG. O.T.	0.1 MG. O.T.	
385	−		−	−
234	−	−		−
147	−	Not done		−
1	−	−		+ (miliary tuberculosis)
34	+		+	+
23	+	Not done		+
2	+	+		+
11	+	Not done		−
1	+		+	−
1	±		−	−
3	±	−		−
1	±		−	−
2	−	+		−
1	−	±		−
1	−		±	−

Among 847 children admitted to the Mount Sinai Hospital, there was only one case with clinical, roentgenographic, or bacteriologic findings

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indicating a tuberculous infection who failed to show a positive reaction to the patch test. This exception was a 19-month-old child with miliary tuberculosis; ten days before he died, the Mantoux test using 1.0 mg. of old tuberculin was negative, as was the patch test.

In this group, both the Mantoux and the patch tests were done and the reactions compared in 666 children. Six hundred and fifty-seven of them showed conformity, and nine no conformity. Among these nine cases showing no agreement, five gave reactions favoring the patch test.

Of these 666 children in whom both tests were carried out, there were 42 positive reactors to the patch test, and 41 positive reactors to the Mantoux test in concentrations of 0.1 or 1.0 mg. of old tuberculin. Some of these reactions were questionable and were probably pseudoreactions.

In the last year, 243 children received the patch test as the first tuberculin test. Only negative reactors to the patch test were retested after from four to six days with the Mantoux test, using 1.0 mg. of old tuberculin. Only two children with a negative patch test subsequently showed a positive reaction to the Mantoux test with 1.0 mg. of old tuberculin; but no tuberculous lesion was found.

Group 2 comprised 540 children from the Sea View Hospital, Staten Island, N. Y., with active tuberculosis. The tuberculin testing was carried out under conditions similar to those of Group 1. The results are tabulated in Table II.

TABLE II

CASES (540)	PATCH TEST	MANTOUX TEST						TBC. FINDINGS
		P.P.D.*		MG. OLD TUBERCULIN				
		I	II	0.001	0.01	0.1	1.0-10.0	
164	+	+						+
2	-	-	-					+
1	+	-						+
1	-	-	+					+
1	+	-	+					+
335	+				+			+
2	-				-			+
16	+					+		+
12	+			+				+
5	-						-	-
1	-				+			+

*In this table, P.P.D. I indicates first strength purified protein derivative; P.P.D. II, second strength purified protein derivative.

Five children of this group were ruled out as nontuberculous, and 535 showed definite tuberculous lesions. Among these, 529 were positive to the patch test, and 530 positive to the Mantoux test with various concentrations of old tuberculin and purified protein derivative, respectively. Of the six patients with active tuberculosis who failed to react to the patch test, four were known to be negative anergic; they also showed, at various occasions, negative reactions to the Mantoux test with

high concentrations of tuberculin. Only two cases were really missed by the patch test. One of them was that of a child with positive anergy who failed to react to the Mantoux test performed with first strength purified protein derivative, but reacted to second strength purified protein derivative. The second negative reactor to the patch test showed a positive reaction to the Mantoux test with 0.01 mg. of old tuberculin. A technical mistake must be assumed.

Group 3.—In the spring of 1938, 613 school children of the Stuyvesant High School, New York, were tested by the New York Department of Health, under the supervision of Dr. A. B. Robins. Dr. Herbert R. Edwards, Director of the Bureau of Tuberculosis, suggested this comparative study and kindly gave permission to use his figures. In contrast to the Groups 1 and 2, this was a mass examination performed in as short a time as possible, with the author present. It was carried out by physicians not yet familiar with the patch test method. The weaker patch test,[2] was used, containing regular old tuberculin. There was only one opportunity to read the reactions, i.e., twenty-four (instead of the usual forty-eight) hours after the removal of the adhesive. Moreover, most of the students went to the gymnasium immediately after the application of the patch test and perspired profusely, thereby impairing the adhesive power of the patch test. Thus, several unfavorable factors affected the outcome of the patch test. Simultaneously with the patch test, the Mantoux test was carried out with the intermediate strength solution (5:10,000) of purified protein derivative or 0.1 mg. of old tuberculin. The results are tabulated in Table III.

TABLE III

CASES (613)	PATCH TEST (WEAKER)	MANTOUX TEST
461	-	-
125	+	+
18	-	+
4	+	-
5	±	-

The tuberculin testing of the children was followed by x-ray examination. Dr. Robins draws the conclusion that "the intradermal tests are somewhat more sensitive than the patch test, but that no significant lesions are missed if patients fail to react positively to either one."

Table IV summarizes results in the three groups, with special consideration of the question of whether or not active tuberculous lesions may be missed by the patch test.

This table shows that, among 2,000 children with 763 positive reactors to tuberculin, three cases with active tuberculosis were missed by the patch test. Two of these failures cannot reasonably be ascribed to an insufficiency of the patch test, but rather to the biologic character

of the tuberculous condition, miliary tuberculosis and positive anergy, respectively.

TABLE IV

GROUP	CASES	POSITIVE REACTORS TO EITHER MANTOUX OR PATCH TEST	CASES WITH ACTIVE TUBERCULOUS LESIONS MISSED BY THE PATCH TEST	REMARKS
1	847	80	1	Case of miliary tuberculosis; Mantoux 1.0 mg. O.T., neg.
2	540	531	2	One case with positive anergy, reacting only to Mantoux with P.P.D. II
3	613	152	0	
Total	2,000	763	3	

No biologic test is 100 per cent reliable. With all due respect to the Mantoux test, it too is not infallible. If the natural limitations of any biologic test are taken into consideration, the tuberculin patch test appears from this survey to be a sufficiently reliable test for case finding.

TABLE V

AUTHOR	CASES	POSITIVE REACTORS TO		MANTOUX CONCENTRATION	REMARKS
		PATCH	MANTOUX		
Taylor	744	218	206	0.1 O.T.	
Steward	96	96	90	0.1 O.T.	
Court	210	129	131	0.1 O.T.	
Saul*	25	25	23	0.1 O.T.	
Greenwald*	404	16	16	0.1 O.T.	
Weiner and Neustadt	257	54	(47) 58	(Pirquet) and 0.1 O.T.	Weaker (about 50 per cent) patch test used
Hart	536	97	100	0.01-1.0 O.T.	Three negative reactors to patch test were only positive to Mantoux with 1.0 mg. O.T.
H. L. K. Shaw*	358	73	81	0.1-1.0 O.T.	
Kerr and Winograd	1,455	213	227	P.P.D. I	Difference attributed by the authors to unsatisfactory technique with the patch test in two groups of children
Leonidoff	200	193	187	P.P.D. I, II	
Total	4,285	1,114	1,119		
Vollmer*					
Mt. Sinai H.	666	42	41	0.1-1.0 O.T.	
Sea View H.	540	529	530	P.P.D. I, II 0.001-10.0 O.T.	
H. Edwards, N. Y. Health Department	613	134	143	P.P.D. 5:10,000 or 0.1 O.T.	Weaker patch test used
Total	1,819	705	714		
Total	6,104	1,819	1,833		0.77% difference
Peck and Wegman†	880	94	319 (131)	P.P.D. II P.P.D. I	70.5% difference 28.3% difference

*Personal communication.

†Separately listed because of unexplained great discrepancy as compared with all other reports.

The author may seem to be unduly partial. His results have been made to appear questionable by a recent publication of Peck and Wegman.[3] Therefore, in Table V, a survey of the literature, including several personal communications not yet published, is placed for comparison with the results of the present publication. A fair agreement exists among the various authors as to the comparative value of the patch test.

Taylor,[4] Steward,[5] Court,[6] Saul,[7] and Greenwald[7] compared the patch test with the Mantoux test using 0.1 mg. of old tuberculin exclusively. Greenwald found 100 per cent agreement; Taylor, Steward, and Saul found the patch test superior, and only Court found it slightly inferior. Weiner and Neustadt[8] came to a somewhat less favorable result, possibly because they used the previous patch test which was weaker than the test in its present form.

Hart,[9] as well as Shaw,[7] compared the patch test with the Mantoux test in increasing concentrations, retesting with 1.0 mg. of old tuberculin those who reacted negatively to the weaker dilutions. Consequently, they found somewhat more reactors to the Mantoux test. As Hart stated, his three cases which showed no conformity were only positive to the Mantoux test with 1.0 mg. of old tuberculin, and negative to weaker dilutions.

The large group of Kerr and Winograd[10] showed an almost complete conformity between the patch and the Mantoux tests, using first strength purified protein derivative. Only in two out of eleven different groups was the patch test inferior. This discrepancy could be traced back by the authors to the fact that in these two groups "alcohol was used in cleansing the arm, and a check-up showed that in nearly every case the adhesive had not stuck properly." Leonidoff[11] used first and second strength solutions of purified protein derivative for comparison. His results appear to be more in favor of the patch test than might reasonably have been expected.

In general, the comparative results of ten different investigators agree with those here reported by the author. In a total number of 6,104 cases, 1,819 positive reactors to the patch test were found, as compared with 1,833 positive reactors to the Mantoux test, including the use of higher tuberculin concentrations (1.0 mg. O.T. and P.P.D. II). The average difference is only 0.77 per cent. If the positive reactors to the patch test are compared only with the positive reactors to the Mantoux test using no higher concentrations than 0.1 mg. of old tuberculin or first strength purified protein derivative, 100 per cent agreement results.

In complete contrast to these unanimously favorable reports, Peck and Wegman[3] found 28.3 and 70.5 per cent discrepancy, respectively, between the patch and the Mantoux tests with first and second

strength solutions of purified protein derivative. I do not believe that the patch test itself is responsible for the poor results. In the case of one investigator who had similar disappointing findings and who communicated with me, I was able to trace the error, the elimination of which brought his results in line with the others.

Various mistakes which may discredit the patch test are possible in such a comparative study. They can occur in connection with the Mantoux as well as with the patch test, both leading to an erroneously unfavorable evaluation of the patch test.

Errors in making up the tuberculin dilution or contamination of the solution, as well as wrong interpretation of the skin reactions, may bring about "too good" results with the Mantoux test. On the other hand, the results with the patch test can be materially impaired by the following factors:

1. A self-made patch test containing weaker tuberculin may have been used.

2. Old patches may be used. Whereas the tuberculin is almost indefinitely stable, the adhesive may lose its adhesive power after one or more years if it is not kept in a cool place.

3. The skin may not be properly cleaned and defatted (preferably done with acetone).

4. The adhesive may not be carefully sealed around the patches on the skin.

5. An improper skin site may be chosen for the application of the test.

6. The patch may be removed or the reaction read before the due time.

Of course, such mistakes cannot reasonably be ascribed to the patch test method.

However, two criticisms have been brought forth which are both acceptable, even if they seem to be contradictory. Some investigators have complained of too strong, others of too weak, reactions obtained with the patch test. Undoubtedly, very strong reactions with blisterous skin eruptions occasionally occur in cases with active tuberculosis and high sensitivity to tuberculin; they occur in the same cases which frequently react to the Mantoux test with 0.1 mg. of old tuberculin or intermediate strength purified protein derivative with a severe local reaction or even necrosis and lymphangitis.

Those severe reactions can be avoided with the patch test as well as with the Mantoux test. Whenever active tuberculosis is suspected, a preliminary Mantoux test with weaker dilutions of tuberculin (1:10,000 or 1:100,000) is usually carried out. On the other hand, the strength of the patch test can be modified either by variation of the tuberculin concentration in the patches[12] or by variation of the length of time of application. The latter way appears more practical.

In a group of sixty-four children with active tuberculosis, Dr. E. W. Goldberger compared the Mantoux test using various tuberculin concentrations with the patch test applied for various lengths of time. According to their sensitivity to tuberculin known from previous tuberculin tests, four different groups were formed. The Mantoux test using various dilutions was simultaneously carried out, and the reactions were compared with the patch test applied for various lengths of time (Table VI).

Table VI shows:

1. Positive reactors to the Mantoux test with 0.01 mg. of old tuberculin did not fail to react to the patch test applied for only twenty-four hours.
2. Positive reactors to the Mantoux test with 0.001 mg. of old tuberculin did not fail to react to the patch test applied for only twelve or eighteen hours.
3. Positive reactors to the Mantoux test with 0.0001 mg. of old tuberculin did not fail to react to the patch test applied for only three, six, or twelve hours.

Consequently, in order to avoid too strong reactions in cases suspected of active tuberculosis, a preliminary patch test can be done. An ordinary patch test is used, but is applied for only six, twelve, or twenty-four hours instead of forty-eight hours. Negative reactors to this preliminary test should be retested with the patch test applied for forty-eight hours.

The second criticism refers to the weakness of some patch test reactions and to the fact that some investigators found somewhat fewer reactors to the patch than to the Mantoux test. This objection could easily be overcome by the use of a higher tuberculin concentration in a smaller piece of filter paper. For experimental purposes, the same amount of tuberculin usually absorbed by a 10 × 10 mm. square was placed on a 10 × 5 mm. rectangle of filter paper, not only to obtain a stronger reaction on a smaller area of skin, but also to assure better contact, because of the additional 1.5 sq. cm. of adhesive surface.

With this modification, more reactors were found to the patch test than to the Mantoux test with 0.1 mg. of old tuberculin. There was, however, not sufficient reason to make use of this modification. The tuberculin patch test in its present form, using tuberculin from synthetic media, has proved satisfactory for its practical purpose.

The patch test does not meet with the rigid requirements of statisticians who wish to discover the greatest possible number of positive reactors, even though some of the reactions prove to be pseudoreactions which merely cause anxiety and unnecessary expense. The patch test does claim to make tuberculin testing a simple, innocuous, and generally acceptable procedure which reliably discovers all cases worth singling out for isolation, treatment, or observation. Whether this statement should be reserved only to the period of childhood, and cannot be applied to later periods of life, I am not prepared to say.

TABLE VI

GROUP	CASES	PATCH TEST APPLICATION TIME IN HOURS									MANTOUX TEST MG. O.T.			
		48	36	30	24	18	12	9	6	3	0.1	0.01	0.001	0.0001
I. Low sensitivity	16	+	+	+	+						+	+		
II. Moderate sensitivity	14			+	+	+						+	+	
	2			+	+	+						+	-	
III. High sensitivity	11				+	+	+						+	+
	1				+	+	+						+	-
IV. Very high sensitivity	19							+	+	+				+
	1							+	+	-				±

SUMMARY

The value of the tuberculin patch test in case finding has been studied in three groups of children, totalling 2,000 cases.

Among 847 children admitted to the Mount Sinai Hospital, there was only one case with clinical, roentgenographic, or bacteriologic findings indicating a tuberculous infection which failed to show a positive reaction to the patch test. This exception was a child with miliary tuberculosis in whom the Mantoux test with 1.0 mg. of old tuberculin was also negative.

Among 540 children in the Sea View Hospital, 535 had active tuberculous lesions, and 529 of the latter were positive to the patch test. Of the six cases who failed to react to the patch test, four were known to be negative anergic and also to show negative reactions to the Mantoux test with high tuberculin concentrations. Only two cases were really missed by the patch test; one of them was a child with anergy who reacted only to the Mantoux test with second strength purified protein derivative.

A mass examination of 613 high school students was carried out by the New York Health Department with the Mantoux test, the patch test, and x-ray examinations. No significant lesions were missed if patients failed to react positively to either the patch or Mantoux test.

Among 2,000 children with 763 positive reactors to tuberculin, three cases with active tuberculosis were missed by the patch test, one of which was missed also by the Mantoux test with 1.0 mg. of old tuberculin. Two of the failures cannot reasonably be ascribed to an insufficiency of the patch test but rather to the biologic character of the tuberculous condition, miliary tuberculosis and positive anergy, respectively. From this survey, the tuberculin patch test appears to be sufficiently reliable for case finding.

A survey of the literature on the patch test is given, including several personal communications. Ten different investigators made comparative studies in 4,285 cases and found, 1,114 positive reactors to the patch test as compared with 1,119 positive reactors to the Mantoux test. These results agreed with those reported by the author. In a total of 6,104 cases, 1,819 were positive to the patch test, and 1,833 to the Mantoux test including the use of higher tuberculin concentrations. The average difference was 0.77 per cent in favor of the Mantoux test. There was 100 per cent agreement between the number of positive reactors to the patch test and positive reactors to the Mantoux test with 0.1 mg. old tuberculin or first strength purified protein derivative.

In contrast to this favorable evaluation of the patch test, Peck and Wegman found 28.3 and 70.5 per cent discrepancy, respectively, when

the Mantoux test using first and second strength purified protein derivative was compared with the patch test.* The reasons for these findings are not known. The possible errors are enumerated.

In order to avoid too strong reactions to the patch test in cases of active tuberculosis, a preliminary patch test can be carried out which is applied for only six to twenty-four, instead of forty-eight hours.

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*Recently, an identical study of 712 cases was carried out by Pearse, Fried, and Glover,[13] and another study of 2,224 high school children by Logie, Spoto, Garcia, and Kupper.[7] In both series, the patch test in its present form was found superior to the Mantoux test with first and second strength purified protein derivative.

CREEPING ERUPTION (ANKYLOSTOMA BRAZILIENSE INFESTATION) WITH SPONTANEOUS REMISSIONS AND RECURRENCES

Report of Two Cases

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THE clinical studies of Kirby-Smith[1] and his associates and the experimental observation of Shelmire[2] apparently have established the etiological agent of creeping eruption as the larvae of *Ankylostoma braziliense*. The early signs and symptoms produced by these larvae have been described by Shelmire.[2] His observations were made on a group of human volunteers.

The present paper is a report of two cases of creeping eruption observed over a period of one and one-half years. It is interesting that the patients were infested while on a vacation on the west coast of Florida, after which they returned to their home in Tennessee. As far as I know, no case of *Ankylostoma braziliense* infestation has ever been observed to develop in the latter state. Because of this, the clinical manifestations apparently can be attributed to the infestation which developed at a specific time.

CASE REPORTS

Two girls, M. V., aged 3½ years, and A. L., aged 2 years, accompanied their parents to the beach and reached there July 16, 1938. Their cottage was located in a grove with many trees. The soil was sandy. Many small collections of water were present along the beach. Several native dogs and cats had access to the grounds at all times. The children played in the small pools of water and in the sand without shoes.

On July 28 both children showed small blebs upon each foot. These blebs were frequently tortuous, resembling the raised burrow left by a meadow mole in a freshly packed lawn. The blebs usually were filled with thin clear serum. The fluid in some, however, was thick and contained white flakes. The lesions were almost constantly scratched by the children, and sleep was interrupted both day and night during the first two weeks of the infestation.

The lesions were localized on the feet. They were present on the dorsum, on the toes, and on the plantar surfaces of each foot. The blebs progressed in length from day to day. They either ruptured spontaneously, or the fluid was absorbed. The many burrows and blebs suggested the presence of several larvae in the feet of both children. These lesions were treated during the first two weeks by the local application of ethyl acetate and by freezing with ethyl chloride.

On August 16 the children left for their home in Tennessee. The blebs and burrows continued to appear and to disappear. Itching was much less severe, however, than during the first week of the infestation.

Localized areas on the feet were frozen with ethyl chloride at different intervals during the following month. On some occasions as many as three areas were frozen. Apparently some of the larvae were killed by this freezing, but blebs and burrows continued to appear over the feet. The itching greatly decreased as time progressed.

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Lesions were still present on the feet on September 15. The frequency with which the blebs and burrows appeared, progressively decreased, however, during the following month. In November, I considered both the children completely well.

On December 1 the skin on the medial side of A. L.'s right foot became hyperemic, and subsequently a bleb and a burrow developed. The epithelium in this area became dry and desquamated, but after one week the lesion had healed completely.

On December 23 an area of approximately 2 x 2 cm. on the medial side of M. V.'s right foot was blanched when she awoke in the morning. The area became hyperemic after a few hours and remained red for approximately ten days (Fig. 1). The lesion was frequently scratched during the first day; however, the sensation of itching rapidly disappeared. Neither a bleb nor any desquamation of the epithelium occurred in this area.

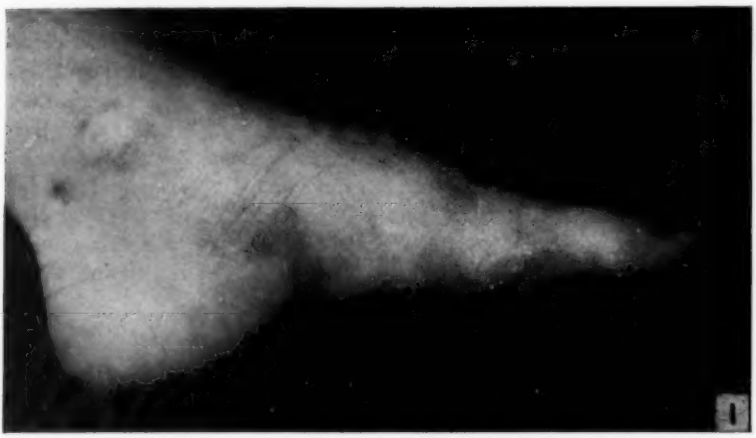

Fig. 1.—Photograph showing area of hyperemia on the medial side of M. V.'s right foot in the area of the arch. This type of lesion was frequently observed a few months after the original infestation.

On Jan. 5, 1939, a localized red area of approximately 2 x 3 mm. developed on A. L.'s right buttock, approximately 3 cm. lateral to the anus. The lesion gradually increased in size, and the epithelium soon desquamated. A small amount of serum exuded from this lesion. Two weeks later I examined the buttocks and found a burrow 1.5 cm. in length. This lesion resembled in every way those previously located on the feet, but there was only a little itching.

There were several hyperemic areas on the dorsum of A. L.'s right foot and around her toes on January 29. There was one indefinite burrow on the dorsum of her foot. The skin in focal areas on the right buttock had desquamated by this time.

Stools from both children were examined on February 1, but they were negative for any intestinal parasites.

On February 15, a burrow, typical of the larvae, appeared on A. L.'s right buttock (Fig. 2). There were no lesions on the feet at this time, and the lesions on the buttock gradually disappeared in a manner similar to the previous ones.

The morning of April 3, A. L. complained of an itching sensation on the medial side of the arch of her right foot. This area was hyperemic, and there were several small blebs present. This area remained red and itched for approximately thirty-six hours. After forty-eight hours the area appeared normal. No characteristic burrow developed during this time.

On April 17, M. V. had a small blanched area on the medial side of her right heel. This was surrounded by a zone of hyperemia approximately 1.5 cm. in diameter. This

lesion remained for forty-eight hours and then completely disappeared. The itching was less severe than that which formerly accompanied the lesions.

A. L. had a recurrence of the lesions on the right foot on May 16.

On June 11 the two children left for the east coast of Florida for two months' vacation. Six months have now passed, and neither of them has shown any lesions which would suggest a recurrence of the *Ankylostoma braziliense* infestation.

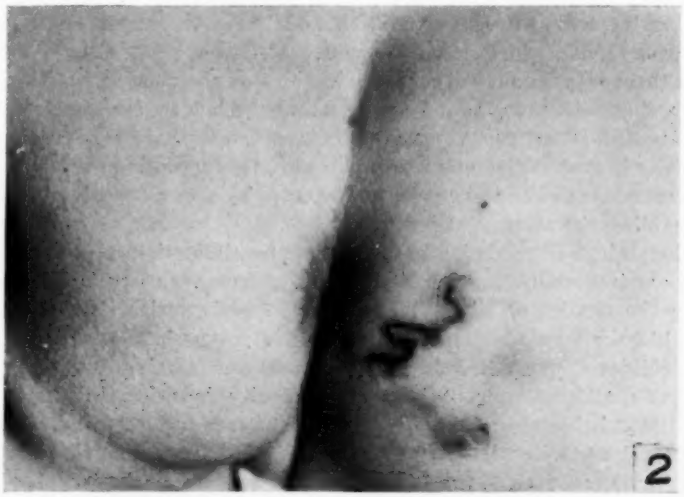

Fig. 2.—The burrow on the buttock is the same type as those on the feet. This one occurred six months following the original lesions on the feet.

DISCUSSION

The two cases of *Ankylostoma braziliense* infestation reported here show a similar clinical course, except for the fact that one of the children had a lesion on the buttocks six months after the original lesion had appeared on the feet. Since the children left the coast of Florida following the infestation and lived in a section of the country in which cases of *Ankylostoma braziliense* infestation have not been observed, it appears most likely that they retained the original larvae in their tissue over a period of approximately ten months.

The blanching and hyperemia which frequently developed on the feet after the first few months apparently could not be considered as a specific lesion produced by this larva. However, in view of the preceding and the subsequent signs and symptoms, it appears most likely that this lesion did result from the larvae of *Ankylostoma braziliense*.

The occurrence of a typical burrow on the buttocks of one of these children six months after leaving the beach offers an opportunity for speculation. Did the larva enter this area of tissue six months previously and remain dormant, or did it extend from the foot to the buttocks through the lymphatics or directly through the tissues? There were no lesions during the period of observation to suggest that such an extension did occur. There is no indication that the larvae were

present in the gastrointestinal tract and passed from there to the tissues in the buttocks. In view of our present knowledge of *Ankylostoma braziliense,* it would seem impossible to state how the larvae came to be present in the buttocks of this child. Shelmire[2] observed a delay of two weeks in the migration of the larvae in one patient in a group of eighteen human volunteers infested experimentally. This is the longest interval between infestation and the development of clinical symptoms with which I am familiar. McCarthy[3] has observed also that there may be no subjective symptoms at the time of infestation. From these observations it is evident that the larvae, for some reason, may rest dormant for a period of several weeks before migration is actually begun. Once migration is begun, it is more intense at night. The movement of the larvae is accompanied by a marked stinging pain resembling the sting of a bee.

The periods of remission in the clinical manifestation of this infestation are interesting in view of therapy. There seems to be no doubt from the studies of Kirby-Smith[1, 4] that freezing with ethyl chloride will kill the larvae. No doubt some of the larvae in the feet of these two children were killed during the process of freezing, but some apparently died spontaneously. The difficulty in using this form of treatment is in determining, first, the exact area to freeze and, second, the depth of tissue necessary to be frozen. It is very difficult to freeze the plantar surface of the feet sufficiently to destroy the larvae. The probability of a secondary bacterial infection in the ulcerated areas produced by freezing must always be considered.

Kirby-Smith and associates[4] have described the larvae of *Ankylostoma braziliense.* They have also discussed the differences between this larva and others which may be found in the human being. The histologic lesions produced by the larva of *Ankylostoma braziliense* in the skin have been described.[4] McCarthy[3] and Kirby-Smith have also studied the life cycle of the larva.

SUMMARY

Two cases of skin infestation with the larvae of *Ankylostoma braziliense* are reported. The cases are interesting because of the remissions which occurred over a period of ten months and because of the observation of a lesion occurring in a portion of the body distal to the primary site six months following the original infestation.

The two cases reported here are those of the children of the writer. I wish to thank the members of the staff of Vanderbilt Hospital for their kindness to me and to the children while these lesions were being observed.

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Special Article

INFLUENCE OF MOTHERS' ATTITUDES ON MENTAL HEALTH

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YOUNG Mrs. B., due for delivery, received a wire from her obstetrician urging her to get back to the city some hours distant from the recreation spot where, despite her advanced pregnancy, she had been enjoying active sports. The doctor feared that labor might set in while his patient was too far from the hospital where arrangements had been made for her care. Mrs. B. was not impressed by his urging. Labor began that very night, and her first child, a son, was delivered in the nearby small rural hospital. After an uneventful confinement Mrs. B. and the child were transferred to their home. Mrs. B. quickly was up and about; she made no effort to nurse the child who was cared for by a nurse and the maternal grandmother. The child did not thrive despite the benefit of good feeding advice. After a considerable period during which various formulas were tried and the family were on edge because of the failure of the child to make progress, Mrs. B. decided to take matters into her own hands. She claims the child throve on her feeding methods. Some years later she explained her attitude as follows: "I didn't know or care anything about children, but I had raised many a litter of pups. I figured that if you followed the same tactics with a baby as with a pup, it probably would work. The others had tried their hand and seemed to get nowhere so I thought there was nothing to lose. I fed him about the way I had fed young puppies, and he got along all right." In speaking further about her delay in returning to the city toward the end of her period of pregnancy, Mrs. B.'s comments were substantially as follows: "I never was interested in children and I didn't like being pregnant. I was an experienced horsewoman and rode until very late in the pregnancy. No one could tell I was pregnant. After the child was born I felt as though I had laid an egg, and I was through with it." Mrs. B. subsequently was divorced from her husband; the child lived chiefly with the maternal grandparents. He grew to be an adventuresome, heedless, fearless child, at the age of 6 years running away from home frequently, subjecting himself to actual physical hazards. He presented the greatest problem in his lack of control, was a trial in school where he would conform

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to no routine and would have things his own way; the "give and take" that children are capable of learning and enjoying seemed to have no meaning for him.

Mrs. R. and her daughter presented a sharply contrasting picture. The child was affectionate and clinging. Always she constituted a problem in eating, just picking at food, restless and overactive at meals. The mother would divert her from the food by endless telling of tales. When the child began school, the mother brought her there and called for her despite the proximity of the school to the home. She supervised the child's luncheons at school and otherwise continued to concern herself with the child in the school just as she had at home.

Mrs. R. was married over ten years before she became pregnant and had given up all hope of having a child. She finally became pregnant after a corrective operation. Mrs. R. could not believe she really was pregnant and was afraid the child would be born dead. The labor was prolonged, the child was colicky and difficult to feed and care for. The mother was so anxious that for a long time the father had to assume major responsibility for the child's routine care. The parents gave up much of their freedom, and their personal and social activities were greatly restricted. For years they felt they could not be away from the home and would trust the child to no one else, not even for a single evening.

These two extremes present the great range of attitudes toward children evidenced by mothers. These extremes of rejection on the one hand, overattachment on the other, give us opportunity to observe effects of mothers' attitudes that might not be readily discernible in less obvious instances. It has long been apparent that what the mother does, and how she does it, are of primary importance in the early establishment of good or poor habits of eating, sleeping, and elimination. Not so readily apparent have been the more fundamental attitudes and motivating forces that result in sharply contrasting experiences. One totally inexperienced mother will go along happily and successfully in the care of a new infant while another mother, starting with an equally healthy infant, incounters increasing difficulties. I must state at once that we are not overlooking those constitutional and physical peculiarities that make for fundamental differences in the response of an infant to a given food and to given training tactics. Every infant will present problems requiring special knowledge of the physical organism and perhaps special skill in management. In this article, however, we are confining our interest to the mother's particular contribution to the creation and solution of the problems. We are attempting to inspect the differences we note in mothers' ability to apply the information or instructions given them by their pediatricians and to take advantage of their own talents and skills in the care of their children.

Freedom from irritation and tension constitutes an important element in the healthy development and growth of any organism. The period of human infancy is prolonged, and the continuous factor of major importance in determining the nature of the development during that infancy is the relationship with the mother. To be sure, this becomes, or normally should become, of decreasing importance, but certainly is crucial during the earlier years.

We are not speaking here in general terms, but quite specifically of the fact that the emotional and social development of the child normally follows a definite course and that this development is of the nature of a changing relationship primarily with the mother, secondarily with the father. While the details of this course of development must be discussed elsewhere, we must here note at least that it includes the development initially of an exclusive and dependent attachment to the mother, who cares for the child's physical needs. There follows a giving up of this exclusive dependence on the mother in favor of a relationship that includes other persons and involves gradually some responsible activity on the part of the child. During this period, the conduct and attitude of the mother may be conducive toward favorable progress in this course of development or may be such as to disturb or to impede.

The pediatrician is in a good position to observe and understand not only those irritations that are dependent upon disease, nutritional or other disturbances, but also those that are inherent in the relation of the mother to the child. Most obvious are those problems that are dependent upon the direct anxiety of a young and inexperienced but emotionally healthy mother who requires only instruction and guidance from the pediatrist. These fortunately constitute a fairly large proportion of the mothers who seek the pediatrician's advice. But the discriminating pediatrist will attempt to understand in detail the situation of the less successful mother.

With no attempt at completeness or scientific classification, it may be of some value to list some of the commonest attitudes observed among mothers who encounter difficulties with their children.

1. Mothers who overprotect their children
   a. "Pure" overprotection—a genuine overconcern for the welfare of the child, as Mrs. R. above.
   b. Compensatory overprotection.
      Here an overprotective attitude masks some rejection of the child.
2. Mothers who are closely attached to their children for reasons not related to the children's needs, but the mothers'.
   a. The emotionally deprived mother who turns to the child for gratification of her own need for affection.

b. The ambitious but frustrated mother who seeks to gratify her own ambitions through the child's accomplishments.

3. Mothers who reject their children, consciously or unconsciously.

   The numerous reasons for such rejection cannot here be discussed adequately. They range from fundamental resentment at being forced to accept a feminine role, to specific traumatic experiences, e.g., having herself experienced rejection during childhood.

4. Ambivalent attitudes, i.e., conflicting attitudes of acceptance and rejection.

   This "classification" overlaps the above (as 1 a), but is included because ambivalent attitudes, not recognized as such, create confusion for both mother and child and sometimes for the physician.

The child learns how he may deal with and relate himself to other persons primarily through his experience in relating himself to his parents. This earliest social experience fairly determines the general pattern of his subsequent social and emotional responsiveness. The most favorable situation the child can encounter is one in which there is a positive, warm, and affectionate attitude toward him, tempered by an awareness on the part of the parents of what the child needs and can constructively use in his relationship to them. Beginning with that complete protection offered by the mother when the child is still within the womb, one expects the gradual withdrawal of the protective indulgences the child no longer needs, but the continuous maintenance of a positive attitude of love and sympathetic support. The child is thus helped toward an increasing independence and self-reliance. This process, however, can be too fast or too slow, and there are consequences that reflect themselves in behavior and in character development of the child accordingly. Mrs. B. above had an attitude toward her child's needs that might be appropriate for a young puppy who requires only the briefest period of maternal care, after which he fends for himself. Her complete withdrawal from the child gave him no opportunity to have the satisfaction that comes with reasonable maternal care, nor to discover how a mature adult conducts herself toward a weaker and dependent creature. Being a vigorous and robust youngster, he found it easy to dominate his indulgent grandparents. He aggressively and defiantly set out to explore the world in a manner that threatened to cut short his career through the sheer hazards to which he subjected himself. We see here the early steps toward a nonsocial life that might easily be expected to lead to a career of delinquency. Not all children neglected by the mother respond in this way, to be sure. The more usual response is

a deep sense of injury and resentment which expresses itself in a hostile asocial attitude, with at times a paranoid coloring (no one loves me, everyone is against me) or an eternal seeking for the supportive maternal love, the need for which never has been gratified (in the adult—the alcoholic). These reactions can be observed with monotonous repetition in the clinical study of neurotic adults as well as quite directly in the behavior of children. With Mrs. R.'s daughter, the tendency to the prolongation of infancy results in behavior that contrasts strongly with that of the predelinquent youngster too early thrown on his own resources. Here the clinging to infancy, the reluctance to take forward steps in the direction of normal social life, is familiar to every pediatrician.

Determining the essential attitude of the mother toward her children constitutes an important diagnostic step. It gives the necessary clue to an understanding of the child's behavior on the one hand, and enables one to gauge the problems the child is meeting in the development of his emotional life. Also, clinical experience now guides us in our judgments as to the steps to be taken in the interest of the child's mental health. So often we find that perfectly good advice falls on barren ground, as the mother finds it impossible successfully to apply the measures advocated by the physician. In many instances she finds good reasons to avoid doing so. The problem for the pediatrician varies widely according to this factor. It may not be apparent on the surface that a mother quite completely rejects her child; usually she is unable to recognize this. The limitations of this article do not permit extensive discussion of the curious problem of rejection-overattachment, in which the unconscious efforts of the mother to hide from herself attitudes which she herself would condemn play an important role.

Either of these extremes, rejection or overattachment, makes for difficulty in influencing the mother or the child constructively. A wise mental health adviser, however, can go far, with patience and persistence, in helping prevent the unfavorable effects of these unfortunate relationships. With the rejected child, often the therapist must play an active role in providing the child temporarily with the sympathetic, supportive understanding he does not get from a parent and helping bridge the gap to relationships with other persons who can in part at least make up for the deficiency he feels in his family situation. Such rejected children at times are difficult to treat, since they find it difficult to relate themselves in a positive manner to anyone. Where one is dealing with neurotic overattachment, again there are great difficulties in winning either mother or child to an understanding of the needs of the latter. Fortunately, however, the pediatrician usually does not find himself faced with the extremes of these reactions. He may be dealing simply with the anxieties of healthy

parents who, for realistic reasons and through lack of knowledge, overindulge a child as did Mrs. R. and her husband. Such parents are quite capable of understanding the psychological problem once it is clearly enunciated by the physician and are glad to follow his advice and to rely on his reassurances. Also many parents whose attitudes are best characterized as ambivalent can be helped to an understanding of the conflictful character of their feelings toward the child and the more constructive aspects of their relationship strengthened. Many a mother needs the relief of discovering that she is trying too hard to meet her child's needs. Inwardly she may have been resenting this fact for a long time, and yet feel driven to tax herself beyond the necessities and beyond her capacity. A mother may need help in facing the fact that for her there are some fundamental dissatisfactions in dealing with her child, whether these be provoked by characteristics, capacities, or incapacities of the child, or spring from other sources. Defining a problem is always the first step in its solution. This holds quite as well in the problem of a mother's attitudes toward her child and the effect these have on the child's development, as they do in the solution of the other medical problems with which the physician is faced.

Critical Review

DISORDERS OF THE INTERNAL GLAND SECRETION IN CHILDREN

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DURING the past few years the entire aspect of endocrinology has been changed by the isolation and synthesis of crystalline pure hormones. Most of these are in the class of so-called sex and adrenal hormones. They are steroid substances related to cholesterol, and they differ chemically from the protein pituitary hormones which have not yet been isolated in pure form. The pharmacologic effects of these powerful crystalline substances have received wide attention in the recent literature. As the knowledge of their action broadens, new clinical uses are proposed. Up to the present there has been little danger in the use of various hormone preparations because they were relatively impure and impotent. The crystalline pure preparations, however, are extremely potent even in small doses and must, therefore, be administered cautiously. In this review an attempt has been made to summarize some of the newer knowledge concerning the action and metabolism of the hormones. Inasmuch as it is the function of a reviewer to review, the opinion of the authors has been expressed freely on certain subjects. Wherever this has been done, they have tried to make it clear that they were so doing.

Thyroid.—Evans, Simpson, and Pencharz[1] have studied the relationship between the thyroid and the growth-promoting effects of the pituitary on rats. Growth promotion in excess of normal secured by anterior pituitary extracts is not dependent upon the presence of the thyroid, but is greater when the thyroid is present or when thyroid is administered to animals whose thyroids and/or pituitaries have been removed. The reviewers believe this work may explain why thyroid medication sometimes stimulates dwarfed children to grow. Hyperthyroidism causes tremendous reductions in the ascorbic acid content of the endocrine glands and other tissues.[2] The administration of vitamin C counteracts this to a large extent.

Means and Lerman[3] have clarified the metabolism of the thyroid hormone in the body. They find that the basal metabolism falls as circulating thyroxine decays. A similar fall in metabolism is observed after the administration of iodine in thyrotoxicosis. The similarity of the two curves suggests that iodine stops the liberation of the thyroid principle from the gland. Castleman and Hertz[4] report from the same clinic a case of pluriglandular insufficiency (proved at post-mortem examination) without cachexia which was believed to be a case of myxedema during life. J. Talbott and Hertz[4] have been struck by the sensitivity of patients with adrenal insufficiency to thyroid extract. In these patients the administration of thyroid may bring on acute symptoms of Addison's disease. According to them, pituitary in-

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sufficiency should be suspected in cases of typical myxedema in which there are earmarks of other endocrine deficiencies such as onset of early amenorrhea (myxedema is usually characterized by metrorrhagia) or signs of adrenal insufficiency. In such cases thyroid should be used cautiously. An excellent and more comprehensive review of the recent advances in diseases of the thyroid gland has been published recently by Means.[5]

OBESITY

Adipose persons have long been divided theoretically into two groups—those who are fat because they eat too much and those who are obese because of some endogenous or endocrine disease. The problem of making the correct diagnosis has troubled many clinicians. Bruch[6] has made some pertinent observations on a group of ordinary fat children. She finds that they are taller than the average for age, that their skeletal age tends to be advanced, and that, as a rule, they develop sexually early rather than late. One of us[7] made similar observations and, in addition, noted that the basal metabolism of the protoplasmic mass[8] was elevated. These findings suggest a simple method for ruling out endocrine deficiency in cases of juvenile obesity. If a fat child is taller than average and if his skeletal age is advanced, it is reasonably good evidence that he is not suffering from deficiency of anterior pituitary or thyroid hormones, because an adequate supply of these hormones appears to be essential to optimal growth and development. Wilder[9] believes that a good many cases of obesity which commonly have been attributed to glandular disturbances are due in reality to lesions in the central nervous system.[10, 11]

Short[12] has described an extraordinary case of obesity in which a loss of 239 pounds was obtained essentially by dietary means. His patient had an elevated basal metabolic rate before treatment. She was placed on a low calorie, relatively high protein diet. As a consequence of the submaintenance diet, her metabolism tended to fall. To counteract this fall in metabolism, thyroid was administered. It was well tolerated after the effect of the reduction diet had manifested itself. The use of thyroid for this specific purpose seems logical to us. It is not indicated for obesity unless the patient is on an effective diet, because these patients ordinarily have an elevated metabolism. The danger of uncontrolled use of thyroid extract in the treatment of obesity is well illustrated by a recently reported case of complete heart block resulting from overdosage.[13]

SEX HORMONES

In recent years it has become clearly recognized that the sex hormones are important not only with respect to the secondary sex organs and reproduction, but that they may exert a profound influence directly or indirectly upon almost every tissue in the body. The male and female hormones will be considered separately.

*Estrogens.**—The ovary produces estradiol†[14] which circulates in the blood stream. In its course through the body, part is inactivated by the liver,[15, 16] and part is excreted in the urine and feces. Estrogens have a definite inhibitory action on the pituitary of rodents, monkeys,

*Substances producing estrous growth in the vagina and uterus of rodents.
†Chemical name for one of the estrogens.

and probably of man, decreasing its activity with regard to its ovarian follicle-stimulating capacity.[17] Large amounts of estrogenic hormone will also inhibit body growth of rats, probably by suppressing the pituitary.[18] In rats, long treatment with the hormone causes a four-fold increase in the size of the pituitary, with marked increase in vascularity which in some cases leads to interlobar hemorrhage and death.[19, 20]

The effect of estrogen upon calcium metabolism and bones has been the subject of several recent papers. In dogs receiving estrogen, precocious closure of the epiphyses has been observed.[21] The same phenomenon has been observed in rats receiving estrogen, but not in rats receiving the male hormone, testosterone propionate.[22] In immature rats the administration of estrogen causes an acceleration in the rate of skeletal maturation.[23] Since thyroid[24] and other hormones influence skeletal maturation and epiphyseal closure, it may be inferred that it is not safe to place too much diagnostic significance on the bone age of children until the various important factors are more clearly understood. In mice and pigeons, the administration of estrogen causes marked endosteal bone formation.[25] Under certain conditions the new bone largely replaces the bone marrow. In human beings, Albright[26] has been unable to produce a significant increase in the density of osteoporotic bones with estrogen. Butler[27] has also been unsuccessful in attempting to treat cases of osteogenesis imperfecta with the hormone.

Estrogens cause rapid involution of the thymus and hypertrophy of the adrenal cortex.[28] According to Gardner,[29] it is unlikely that estrogenic hormone will give rise to cancer except in susceptible persons to whom it has been given in large amounts over a long period of time. In general, it is our opinion that the undesirable effects which may result from the administration of this hormone will be avoided if large amounts are not given over long periods of time.

Nathanson and Weisberger[30] have suggested that estrogenic hormone may be of value in the treatment of leucoplakia buccalis and related lesions. They administered 10,000 international units of estradiol benzoate parenterally six times at two-day intervals. There was definite improvement in 80 per cent of the thirty-eight patients. Mortimer, Wright, and Collip[31] have used estrogen in the treatment of atrophic rhinitis. The hormone (estradiol) is dissolved in olive oil at a concentration of 100 μg. per cubic centimeter. The solution is placed in a nasal atomizer, and about 0.25 c.c. is sprayed into the nostril at each application. They report definite improvement within from two to six weeks.

Progesterone, the corpus luteum hormone, was discussed in the 1939 review.[45]

*Androgens.**—Testosterone† has been isolated from bull testis tissue.[32] Although there is no direct evidence, it is generally assumed at present that the human testis also produces testosterone. It is quite possible that this assumption is entirely erroneous.

The male hormones (androgens), like the estrogens, have many actions in addition to those concerned with sex characters and re-

*Substances which have the ability to cause development of the male sex characters.
†Chemical name for one of the androgens.

production. The known testicular and urinary male hormone preparations and other pure androgens can inhibit the pituitary gonad-stimulating activity. Considerable evidence indicates that another pituitary inhibiting substance is elaborated by the testis tissue. It appears to arise from that part of the testis which is concerned with sperm formation and to have no action upon the accessory sex organs.[33]

General body growth appears to be influenced by the male hormones. Castration of immature rats leads to suppression of growth in length and in weight. Growth in length is more inhibited than in weight.[34] McEwen, Selye, and Collip[35] present evidence to show that, whereas the ovarian hormones inhibit somatic growth of rats, the male hormone, testosterone, in large amounts has no such inhibiting effect. Administration of the hormone does inhibit the growth of the gonads, however. Papanicolaou and Falk[36] have made the interesting finding that androgens cause general muscular enlargement in the guinea pig. This effect was not obtained with the female hormones (estrogen and progesterone).

Heckel[37] has made the observation that the administration of testosterone propionate (synthetic male hormone) caused a marked reduction in the sperm count of a man. The count tended to return toward normal when the hormone therapy was discontinued. Androgens apparently do not have any noticeable effect upon bones. Turner[38] did not observe any advance in epiphyseal union in a patient after forty-five weeks of therapy. He did observe an increase in the amount of hair, enlargement of the larynx, a better distribution of weight, genital development, and increased libido. (These findings have been confirmed by Sexton.[39]) Edwards, Hamilton, and Duntley[40] suggest that testosterone may be a valuable therapeutic agent in the treatment of thromboangiitis obliterans and arteriosclerosis. The hormone apparently increases the cutaneous arterial blood supply. They feel that further investigation is needed before this form of therapy can be generally recommended.

Although androgen therapy will successfully bring about secondary sexual maturity and descent of freely movable testes in genitally hypoplastic males,[41-45] it has been noted that it depresses spermatogenesis[37] and causes a temporary upset in the excretion of urinary androgens[46] in human beings. Furthermore, it will be remembered that these hormones tend to suppress the production of pituitary gonad-stimulating hormones. Consequently, the present reviewers do not recommend that androgens be administered to children until evidence has been presented which makes it certain that the therapy will not defeat the purpose for which it is given. The possibility of using pregnancy urine hormone therapy to stimulate the testes to produce more male hormone has been reviewed elsewhere.[47]

Excretion of Androgens and Estrogens in Urine.—Measurements of the urinary output of sex hormones are being made in rapidly increasing numbers. Methods of measurement are also being improved as knowledge of the urinary hormones increases. Although a few workers in specially equipped laboratories are making detailed analyses, most are working with relatively crude methods. Thus far, the data obtained on children suggest that the excretion varies directly with increasing chronologic age and also with physical maturity. Nathanson,

Towne, and Aub[48] report measurements on the daily excretion of androgens in normal children. They find the excretion of androgens to be slightly higher in the males than in the females of the same age.

It is interesting that both males and females excrete both androgens and estrogens. The recent finding[46, 49, 50, 51] that the administration of male hormone increases the output of both androgens and estrogens may explain why males excrete estrogens. Very high levels of androgen excretion have been found only in cases of hyperplasia or tumor of the adrenal cortex.[51]

Cryptorchidism.—In the past several years there has been a rise in popularity of the endocrine treatment of undescended testicles. It is with interest, therefore, that we read that Johnson[52] and Thompson and Heckel[53] have apparently arrived at the conclusion that the effect of pregnancy urine hormone (A.P.L., etc.) in the treatment of undescended testes appears to be exaggerated. It is quite likely that this material causes descent only of those testes which would descend without treatment at about the time of puberty. Operative procedures are still needed in those cases where mechanical factors prevent descent. Johnson recommends that operation be deferred until the sixteenth year unless it is indicated by some associated condition.

In the foregoing paragraphs no attempt has been made to review the entire field of endocrinology, but rather to focus on some of those aspects which might be of interest to the pediatrician and to bring together some of the recent advances which appeared to be ripe for review. With respect to some of the glands not mentioned here, interesting information is accumulating which should be ready for consideration in the near future.

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Round Table Discussion on Food Allergy in Children

Chairman: Bret Ratner, M.D., New York
Assistants: Lewis Webb Hill, M.D., Boston
Harry H. Donally, M.D., Washington, D.C.
Secretary: Clyde Moore, M.D., Omaha

CHAIRMAN RATNER.—It is with a deep sense of gratification that we are to have the opportunity to discuss with fellow pediatricians the subject of food hypersensitiveness in children.

Former round table discussions devoted to the subject of allergy were of necessity more general than this one is going to be. This one will focus attention on food and will be associated intimately with pediatric practice. We hope that many phases of the subject will be simplified and translated into everyday practice. Let us orient ourselves briefly on the modes of acquisition of food allergy.

Modes of Acquisition

Bret Ratner, M.D., New York

1. Food allergy may have its inception in intrauterine life. The fetus comes in contact with unchanged food proteins that the pregnant woman eats. Cravings of pregnancy are often responsible for the excess of protein food ingested. Some of these proteins escape digestion and may enter the blood stream, thus gaining easy access to the fetal circulation through the highly permeable placental membrane. How otherwise can one explain those cases, which we have all seen, of an infant developing a reaction after getting a new food for the first time?
2. Sensitization via breast milk.
3. Occasional feedings of raw milk during the neonatal period.
4. Raw foods taken during convalescence from disease.
5. Fad diets.
6. Overfeeding.
7. Excessive indulgence in seasonal or bizarre foods.

Pathogenesis.—Under ordinary circumstances ingested food proteins are broken down into amino acids before absorption into the circulation takes place, but there is sufficient evidence to warrant the conclusion that unsplit proteins may enter the blood stream directly from the gastrointestinal tract. Although pathologic lesions of the intestinal tract, stasis, diarrhea, and impaired functioning of the digestive juices may result in abnormal absorption of proteins, it is my belief that, even under normal conditions, the absorption of protein occurs with greater regularity than is generally believed.

Proteins may enter the blood stream from any part of the bowel, even as low down as the rectum. The entrance of these antigens apparently takes place below the stomach, for it is well established that there is little absorption of any kind through the gastric mucous membrane. It is conceivable that antigens in

fluid form can pass the pylorus and enter the small and large intestines in an exceedingly short time. It is also possible that absorption may take place from points as high up as the nasopharynx or mouth.

It is feasible to speculate that throughout the ages animal and man must have developed defense mechanisms, for otherwise we would today be unable to cope adequately with the ingestion of new and strange food proteins.

There are several lines of defense against the invasion of undigested foods into the blood stream.

First Line of Defense Before Entrance Into the Blood Stream.—1. Hydrolysis of food proteins by digestive enzymes.

2. General impermeability of the intestines to colloids.

3. Coagulation of food albumin by heat.

Second Line of Defense After Entrance Into Blood Stream.—1. Development of specific antibodies which may divert the absorbed protein from the sensitized cells, thereby rendering them harmless.

2. The breaking down of proteins due to proteolytic enzymes.

3. Excretion of the foreign protein via the kidney.

The efficiency of one or more of these lines of defense may vary considerably in different persons, making one person more susceptible than another. In the same person, the defense mechanism may function adequately at one time and not at another. This may result from pathologic conditions of the intestinal tract, or because the food was introduced in a raw, or relatively raw, state and in large amounts during particularly vulnerable periods. These periods, as we have mentioned, are during pregnancy, the newborn period, infancy, convalescence, or during periods of great strain or undernutrition.

When any of these defenses fail, the presence of unchanged antigen in the blood stream generates allergic antibodies. These antibodies become attached to various tissue cells. When the particular antigen again enters the body, an allergic reaction may ensue, resulting from interaction of the protein and fixed tissue antibodies.

The allergic clinical picture will depend entirely upon where the reaction between antigen and fixed tissue antibody takes place. Thus, the symptomatology may occur in the gastrointestinal tract, the skin, the respiratory tract, or the nervous system.

Native food proteins, let us remember, enter the circulation of both normal and allergic persons. Why then do some persons become sensitized and others not? This, as yet, cannot be explained fully. However, in a round table discussion, at least some speculation is permissible.

That there are constitutional differences among individual persons, which make some more susceptible to allergy than others, must be granted. Constitutional differences per se are not the decisive factors. In order for a person to become sensitized to a food, it is essential that (1) the protein be soluble, dialyzable, of relatively low molecular weight, and in a native state, (2) the intestinal tract be particularly permeable at the time such a food is ingested, (3) the quantity ingested be large enough for some to escape digestion, and (4) the time intervals at which such foods are consumed bear a relation to periods permitting an adequate incubation to intervene. Thus, if the foods ingested are thoroughly cooked, are not highly diffusible, are taken in moderate amounts, and if there is no increased intestinal permeability due to stasis, diarrhea, or other conditions, allergy will, in all probability, not result from such foods. From the standpoint of temporal factors, were soluble antigens to enter the blood stream in small amounts and at frequent intervals, an immunity to these proteins would probably be established rather than a hypersensitiveness, as has been shown so admirably by the work of

Schloss and his co-workers. The normal absorption of small amounts may conceivably serve the useful purpose of constantly maintaining the body in a state of immunization to foods which are habitually ingested. On the other hand, if highly diffusible native proteins of relatively low molecular weight are taken in large amounts, at frequent or infrequent intervals, and if part of these proteins escape digestion, then such antigens may gain entrance into the body and establish sensitization. Subsequent ingestions of even small amounts of this same antigen may produce allergic manifestations, shock, and even death.

Food sensitization may persist for many years, or immunization may supervene.

This, in short, is the hypothesis of the inciting mechanism of food allergy as I conceive it to be.

With this as a working basis for our discussion, let us proceed to the more practical aspects of the subject. I will now call upon Dr. Hill to tell us something about the diagnosis of allergic manifestations due to food. Dr. Hill will not discuss asthma and eczema, which have been covered so often in previous sessions, but will engage our attention to the more obscure forms occurring in children, always bearing in mind, of course, that asthma, eczema, and urticaria are the most common forms. Dr. Hill, will you continue the discussion?

Diagnosis

Lewis Webb Hill, M.D., Boston

There are a number of manifestations of allergy in infancy and childhood which are less common than eczema, asthma, and hay fever, and because of this relative rarity, we have not as extensive and as accurate information concerning them as we have of the more common manifestations.

Severe hypersensitivity to cow's milk is sometimes seen in early life and is usually first noticed at the time of weaning. Violent symptoms follow the ingestion of only very small amounts, and at least four deaths have been reported. There is always vomiting, sometimes severe diarrhea, sometimes urticaria, and often collapse. These infants may have eczema, but they are more likely to be free from it, and skin tests are more often negative than positive. It is my impression that those who do not have eczema are not likely to have other sensitivities, but I am not entirely sure of this. The sensitivity is either congenital or truly hereditary, or it may be brought about possibly by the taking of cow's milk for a few days during the neonatal period. These infants seem closely analogous to the anaphylactic animal, both in method of exposure and in end result. Those without eczema can almost always take goat's milk without symptoms; those with eczema and positive skin tests are often as sensitive to goat's milk as they are to cow's milk. Both groups can usually be desensitized, and later they can take cow's milk without difficulty. These cases are uncommon. One man with a huge pediatric practice over a period of forty years has seen only nine of them; in twenty-five years of a pediatric practice of modest size, I have seen five.

With the great increase of interest in allergy, it is inevitable that some should have a tendency to magnify its frequency and importance. This is not to be greatly deprecated, for without a spicing of a few high-powered enthusiasts, allergy would lose much of its flavor. It needs also, however, a considerable flavoring of conservatism. All of us who are especially interested in allergy are continually tempted to look for allergy in everything; we must be careful not to see it where it isn't.

It is often said that in bottle-fed infants, colic, chronic vomiting, diarrhea, malnutrition, and pyloric spasm are frequently caused by allergy to cow's milk, and there has developed a not uncommon tendency to immediately assume the allergic origin of some of these disorders, without taking into account more old-fashioned causes. I would certainly be the last one to deny that some of these

disturbances may be caused by allergy, and I firmly believe that they are occasionally so caused, but not *commonly*. We should not forget that plain overfeeding, indigestible masses of curded casein, and gas in the bowel have been causes of abdominal distress in infancy for a good many years.

I am very doubtful that allergy to milk is an important causative factor of malnutrition; most eczematous infants are fat enough, and a high proportion of them are allergic to milk. It is certain that allergy to a food can cause chronic diarrhea, both in infants and children; there are, however, many far more common causes. I have no doubt that vomiting somewhat resembling that seen in pylorospasm may be occasionally caused by milk allergy, but I am very doubtful that the classical hypertonic baby with pylorospasm has anything to do with allergy. It has probably been forgotten long ago that, before the days of thick cereal feeding, whey mixtures were the most successful feedings for such infants, and whey is essentially a 1 per cent lactalbumin solution. Furthermore, at the present time, concentrated whole milk mixtures with thick cereal are almost specific. Please do not think that I am insisting that gastrointestinal disturbances are not sometimes caused by milk allergy; such is far from my belief. Allergy should always be thought of in any obscure gastrointestinal disturbance. I do believe, however, that it is a relatively infrequent cause of such disturbances, and that, at present, its importance is being overemphasized.

Obscure Abdominal Pain.—The older child with recurrent attacks of abdominal pain is surely a difficult diagnostic problem. Every year many such children are admitted to our hospital wards and are put through every possible test, to rule out such conditions as tuberculous abdominal lymph nodes (formerly a common cause), kidney stone, various anatomic defects of the gastrointestinal tract, recurrent appendicitis, and so on. Occasionally some very definite cause is found as a result of all this investigation, but more often the child is sent home undiagnosed. Some of these children have food allergy, but the hospital ward is not a good place to investigate it; if the attacks are at relatively infrequent intervals, it may take months. Scratch tests are of little value here as a rule, and it should not be said that "skin tests are negative" until intracutaneous tests have been done. These also may be negative, however, and the investigation of such patients may take weeks or months of patient study with food diaries and elimination diets, of which I hope Dr. Donnally will speak later. Occasionally the child or mother knows exactly what food or foods cause symptoms; more often they do not. These children may be divided broadly into two groups: those with other allergic symptoms, such as urticaria or asthma, and those without. In the first group, one immediately suspects food allergy as a cause of the pain, and often finds it; in the second group, food allergy should surely be considered, but will not be found so often, and the diagnosis of food allergy should not be made until all other causes have been ruled out, and, even then, only upon the most accurately determined evidence. Furthermore, the relief of symptoms following the removal of a specific food does not necessarily prove food allergy, as Dr. Alvarez of the Mayo Clinic has so well pointed out; there may be other qualities about the food in question, entirely apart from allergy, which may cause distress.

This large group of children with recurrent abdominal pain is to be very obscure and very interesting. I am sure that specific foods account for some of the cases and that the mechanism of the idiosyncrasy is in a few cases allergic.

Cyclic Vomiting.—While I think there can be no doubt that intermittent attacks of vomiting may be caused occasionally by allergy, I cannot believe, as some have thought, that the common syndrome which all of us have always called "cyclic" or "recurrent" vomiting has anything to do with food allergy. The appearance of acetone in the urine often before the vomiting begins, the prompt cure by intravenous glucose and insulin, and the artificial production of the syndrome in susceptible children by a ketogenic diet, all point to it as a metabolic disorder.

Migraine.—Migraine has for many years been an unsolved scourge to patients and doctors alike, and it is entirely to the credit of allergy that at least a fair percentage of cases can now be relieved. In my experience, migraine is not very common in childhood, at least if one adheres to a strict definition, and in the Harriet Lane Home in Baltimore, in 70,000 admissions there were only thirteen cases. In the Boston Children's Hospital wards in the last three years, with 5,248 admissions, there was only one case; in the Out-patient Department, with 14,761 new admissions, thirty-three cases. I mentioned a moment ago "a strict definition of migraine," because some have said that, in childhood migraine, the symptoms of headache were usually lacking, that most attacks of periodic vomiting were in reality migraine and changed to the typical form later in life. If migraine is not caused by food allergy, nobody knows what it is caused by, so every case surely deserves a careful allergic investigation. More information will be gained by intracutaneous than by scratch tests, but sometimes even these are negative, and it is here that the elimination diet and food diary find one of their most useful spheres. My own experience with the allergic investigation of migraine has been too limited to furnish any statistics of value, but what little I have had has been favorable. Those who have had a larger experience have reported about 50 per cent relief following allergic investigation and treatment. For the rest, ergotamine tartrate should not be forgotten.

Urticaria.—If there is a high degree of sensitization to a food, the ingestion of it is often followed by acute urticaria. In infants and children, it has been my experience that egg, fish, nuts, peas, and milk are the most common foods which bring about this response. It must not be forgotten that not infrequently environmental allergens, notably silk and wool, may sometimes cause urticaria by external contact. I can well remember one infant who had an attack every morning at about ten o'clock, shortly after he had taken his orange juice. The mother naturally thought orange juice was the cause, but even after omission of it, the baby had hives. On skin testing, he gave an enormous reaction to silk, and it was found that rubbing on his mother's silk negligee was the entire cause of the hives. Hives are not uncommon shortly following an acute upper respiratory infection, or after the taking of certain drugs, notably aspirin, phenolphthalein, and codeine. Acute urticaria is, as a rule, no great problem. Most of the time, the cause and effect relationship between stimulus and response is obvious. It is probable that most acute urticaria is allergic in mechanism.

Chronic urticaria is, however, a very different proposition, and there is no reason for believing that all, or indeed a majority of cases, are of allergic origin. Skin tests are likely to be negative, nor has the patient any idea as to the cause of the urticaria. Something is causing whealing of the skin; it may be the direct action of products absorbed from the bowel or from foci of infection, or it may have to do with neurogenic influences. In a series of 170 cases studied by Fink and Gay in Baltimore, only thirty-five were found to be due to allergic factors.

Papular Urticaria.—Papular urticaria, or lichen urticatus, is one of the common troublesome things we all see in infants and young children, particularly during the summer months. Many dermatologists believe now that it should not be classed with urticaria, but with prurigo. The characteristic lesion is a small papule, sometimes with a tendency to vesiculation, on an erythematous base. Shortly after the appearance of the lesion, the base disappears, and the papule is left. The distribution is characteristically on the face and the extensor surfaces of the arms and legs—all of which are exposed areas.

The first difficulty about papular urticaria is the diagnosis, for it is often not easy to differentiate from insect bites. Insect bites are, as a rule, larger than the lesions of papular urticaria; there are usually not so many of them, and there is more of a tendency to grouping. Under the hand lens, a small puncture may be

seen on the top of the bite, which is sometimes hemorrhagic. The second difficulty is that nobody knows anything about the cause of papular urticaria. In the last few years, at least four careful pieces of investigation have appeared, and all conclude that the cause is not known, that skin tests are useless, and that omission of specific foods from the diet does no good. My own experience coincides with this.

I have found that painting each lesion with undiluted crude coal tar is good for local treatment; it relieves the itching and promotes the absorption of the lesions.

Allergy is a very young subject, and, furthermore, it is one of the most complicated and least understood branches of medicine. It has made great and important progress. Its clinical manifestations are innumerable; it may affect almost any tissue in the body; it has solved obscure conditions which for many years had been unsolved. If allergy is not to be discredited, however, it must not go too fast: it must not assume too much.

CHAIRMAN RATNER.—I should now like to call upon Dr. Donnally to take up the discussion of the various ways in which we treat the patient with food allergy.

Prevention of Food Allergy

Harry H. Donnally, M.D., Washington, D.C.

When Dr. Ratner reviewed the modes of acquisition of food allergy, there must have occurred to his pediatrist listeners ways and means for circumventing its development, because this is the trend of the pediatrist's mind. Possibly some of you have seen articles by Peshkin, Glaser and Landau, and Ratner, and in the writings of others, discussions of prophylaxis of allergy in infancy and childhood. I will discuss briefly the prevention of the development of food allergy, taking up Chairman Ratner's points seriatim:

"1. Food allergy may have its inception in intrauterine life." It seems that Ratner's proof that this may occur in guinea pigs, and his clinical cases, in which he showed that 30 per cent of pregnant women craved and ate excessively antigenic foods during their pregnancy and that later their babies showed a sensitivity to the same food upon the baby's first contact with it, are widely accepted as the probable course of events. If this is true, women during their pregnancy should eat a well-balanced diet, without excesses, particularly excesses in allergenic foods such as eggs, fish, nuts, shellfish, raw foods, etc.

"2. Sensitization via breast milk." The importance of this factor may not be as great as the intrauterine sensitization. It was established independently by György with a proof similar to my own. Experimentally, it has only been proved for egg white, but other allergenically potent foods may also be eliminated through breast milk. Clinical cases have suggested breast milk as the possible, even probable, source of the allergic sensitization.

An error occurred in the reporting of the panel discussion of allergy at the 1938 meeting of the Academy.*

"3. Occasional feedings of raw milk during the neonatal period." This probably applies also to pasteurized milk and to dry milk, as Ratner has shown. In 1936, Lippard, Schloss, and Johnson demonstrated the temporary absorption of food protein after its initial introduction in ordinary quantities into the diet of the normal

*Dr. Francis Scott Smyth is reported to have said, "The technique Donnally used is not above criticism. He was injecting curds of milk, and I think there is some real room for controversy about that." (J. PEDIAT. 13: 596, 1938.) This is incorrect. Breast milk whey which had been passed through a Seitz filter pad and which came through as a clear yellow fluid of straw color constituted the only breast milk test materials in my study. The processing of the breast milk in preparation for its use as a test agent presumably lowered its content in egg proteins. Dialysis and Seitz filtration probably resulted in the loss of part of the egg white in the breast milk whey. (J. Immunol. 19: 15, 1930.)

infant. In from eight to thirty days antibodies are demonstrable, followed by the disappearance of the antigenic food absorbed. Then follows the disappearance of the antibodies. More recently Lippard has continued the study to show that absorption of protein by the intestine is a physiologic and innocuous process in the majority of normal infants; in others, especially in eczematous infants, it may be associated with the development of a persistent state of tissue hypersensitiveness. He demonstrated this to be the case both for egg white and for cow's milk. Among forty normal infants who had never been fed egg, intracutaneous tests, passive transfer tests, and complement fixation tests were all negative. Among twenty-one eczematous infants who had never been fed egg, one-half showed positive intracutaneous tests, one-third showed passive transfer tests, and one-fourth showed complement fixation tests. It is pertinent to enquire how these eczematous infants who had never been fed egg became sensitized to egg proteins. It seems to me that there are three possible ways this came about:

1. Active sensitization in utero.
2. Sensitization through the breast milk.
3. Sensitization through accidental contacts.

Sensitization in utero and through the breast milk may work together. The infant may have been actively sensitized in utero by egg antigen passing from the maternal to the fetal circulation, and this sensitization may have been maintained by the small quantities of egg antigen passing through the breast milk to the infant. Numerous examples will occur to all of us, in which an infinitesimal amount of protein may cause symptoms in those sensitized or allergic to the protein in question. There is no doubt that a baby may be exposed to egg white ingestion through ordinary contacts. How much of a factor contamination of the mother's lips, mouth, or fingers, and of the dishes, spoons, and other things really is, it is not possible to say.

"4. Raw foods taken during convalescence from disease." Lippard, Schloss, and Johnson concluded that it was a physiologic phenomenon to have food protein absorbed to act as an antigen, following its first ingestion. Besides its demonstration for egg and milk by numerous workers, it has also been demonstrated for fish and nuts by Walzer and others. Fad diets are sometimes composed of raw foods and are frequently unbalanced diets. Besides raw vegetables and fruits, raw meats are sometimes indulged in. Berries of various kinds, peaches, apples, pears, and other fruits are eaten in the raw state. Denaturation is effected by cooking most of these foods in the usual manner, especially boiling in saucepan or double boiler or in the steam cooker. Among exceptions are the following: A child sensitive to ovomucoid may get symptoms from eating a hard-boiled egg, because ovomucoid is not coagulated by heat; cooking fish does not render them less antigenic. Ratner and Gruehl, in their article entitled "Anaphylactogenic Properties of Certain Cereal Foods and Breadstuffs: Allergenic Denaturation by Heat," admit that the methods used in these experiments have no counterpart in the spontaneous sensitization of human beings to grain foods. They believe, however, that these results of experiments with the guinea pig may be translated into terms of allergy in man and applied to the problem of the allergic person hypersensitive to cereal grains. Only a few years ago, my associates on this round table went to the mat on the question of the denaturing of cow's milk by the processing in its evaporation, canning, and heating to 240.8° F. for twenty minutes. Ratner maintained that milk was anaphylactogenically denatured by evaporation, which he has photographed in his excellent film on allergy, while Hill was just as vigorous in his denial that evaporated milk could be used safely in milk-sensitive babies. His words, if I remember them, were, "It simply doesn't work." In the last revision of his article on "Eczema" in Brennemann's *Practice of Pediatrics* a few months back, Hill sticks to his guns. He explains that he cannot prove his point

except clinically, because up to the present time, neither lactalbumin nor casein is produced without contamination of one by the other. Again these specialists disagree when Hill advises, in severe cases of milk sensitivity, the use of one of the soybean flour preparations as a milk substitute. Ratner deplores its use on the ground that soybean is highly antigenic, resistant to high temperatures, and should be avoided when possible.

At last we have an adequate explanation of why fresh fruit should be stewed before being given to babies, i.e., cooking presumably denatures the proteins. Cooked vegetables, when boiled or steam pressure cooked, are believed to be denatured. So far Ratner has not published studies, except of milk denaturation, cereals and breadstuffs, and corn and malt syrups.

The next point that Dr. Ratner indicated was the avoidance of raw foods during convalescence from disease. This is because the intestinal tract following disease is more permeable and absorption of unaltered protein more likely. During diseases and convalescence from them, the infant and young child should have only food denatured by cooking, given in small quantities and well diversified. Ingesting a raw egg stirred into a glass of raw or pasteurized milk invites absorption of egg and milk native proteins, while a hard-boiled egg is generally well tolerated; the exception has been mentioned.

Probably more could well be said about the prophylaxis of food allergies. A popular precooked cereal, containing wheat, oatmeal, cornmeal, alfalfa meal, brewer's yeast, and other things, has been shown by Ratner in his guinea pig work to be nonanaphylactogenic. If this turns out to be nonallergenic for infants, many pediatrists will use it who have advised against it in infantile eczemas and other clinical forms of allergy, because the constituents mentioned may be highly allergenic.

In both prevention and treatment of food allergies, the physician should always remember that he is treating a young, growing person, who thrives best on a well-balanced diet, and he should not lose sight of these principles.

Treatment of Food Allergy.—Enough has already been written about the value of a careful, painstaking history of an allergic child, so I shall mention merely that it is indispensable and must be a continuing matter extending over weeks and months to make it as complete as possible.

A child should be tested fairly completely, certainly with every food that he eats and possibly others with which he becomes in contact, as well as inhalants. There is an exception to this general advice; when it is clear in the history that the child is allergic to certain foods, it would be safer not to test him with these. A mother gave her baby a bag of mixed nuts in the shell to play with. In a few minutes his hands, forearms, and upper and lower eyelids were swollen and edematous. A baby was given a teaspoonful of egg white which he promptly vomited; he broke out with widespread hives and went to sleep and remained as though drugged for several hours, probably from edema of the brain. Instances of exquisite food allergy could be multiplied. Such babies should not be tested directly. Passive transfer of their serum to healthy adults would satisfy the physician's scientific curiosity, but this is scarcely necessary. This again emphasizes the importance of a continuing, calm enquiry about the patient. Many of the leading allergists have at one time written on the theme of taking the history for allergic patients.

All foods giving marked, moderate, and slight skin reactions should be eliminated, at least temporarily, not forgetting that we are primarily physicians, and not only skin testers; nor should we forget that it is not sensible to eliminate from a child's diet for a long period milk, wheat, rice, eggs, oranges, tomatoes, cod liver and halibut-liver oils, and so forth, even though ascorbic acid, thiamin, and vitamin D concentrates are given. As soon as possible, one allergenically denatured

food after another should be added at from three- to seven-day intervals, after a thorough tryout. Only one food should be added at a time; e.g., it is better to add puffed wheat, which contains only wheat, than to add denatured bread or melba toast, which generally contains wheat, milk, and yeast, all at times potent allergens. One bears in mind also that gliadins of wheat and rye are identical allergically. But there is a popular rye cracker which generally can be used, especially if it is baked the second time. This makes it crisp and adds to its palatability. Ratner has published a list of allergenically denatured cereals and breadstuffs, based on the absence of anaphylactogenicity.

If a child cannot take evaporated milk and remain free of symptoms, such milk may not produce symptoms if a can is placed in a pan of water and boiled to again coagulate the soluble proteins. Unless a child is sensitive to casein, which is generally not the case, he is likely not to be sensitive to goat's milk. Some children dislike the taste of goat's milk, as much as one dislikes the smell of the daddy goat.

The principles which I have found most successful are the trial diet, as shown with a diary of foods taken and a diary of symptoms. It has been well established that a patient hypersensitive to a food may take it three times a day without symptoms for two or three days, and that then the symptoms caused by it may make their appearance. Hence, there is the necessity for adding to the diet a single food element, and feeding it every day without symptoms for from three to seven days before adding another. Then one could try adding to the diet foods which had produced only slight skin reactions.

By managing the diet of one's patient in this way, one is likely to detect foods which do not produce as much as even a slight skin reaction. By advancing through foods less and less denatured, one often arrives in the course of from three to six months to the point of taking the cooked food in question. Thus, one advances from evaporated goat's milk, to evaporated milk diluted with water, to boiled cow's milk, and finally to pasteurized milk.

Removal for a few months of a food to which the child is hypersensitive is sometimes all that is necessary to cause him to lose his hypersensitiveness.

Various methods of feeding for desensitization have been in use, and, for the most part, they succeed, if one has the patience, for example, to dilute milk a thousand times and give a drop on the first day, 2 drops on the second day, and so on until the child can take an ounce, after which the amount may be increased rapidly. The same principles apply to foods other than milk, such as orange juice, tomato juice, and so on.

In children, I should not favor the hypodermic injection of food in order to bring about tolerance. It is a risky thing to do and, generally, unnecessary.

CHAIRMAN RATNER.—You have heard from Dr. Hill that the reactions to specific foods are at times so obvious that the immediate response of vomiting or the occurrence of urticaria following the ingestion of a particular food is insufficient for the establishment of an accurate diagnosis. Yet, the manifestations may be delayed for so many hours after ingestion that it is well nigh impossible to associate the symptoms with the intake of any certain food. You have heard from Dr. Donnally that in the majority of cases of food allergy, where the manifestations are respiratory or endermal, positive allergic skin reactions may be obtained to the offending food, and proper elimination of the incriminating substance can be accomplished with a great degree of accuracy. There are a large number of food-sensitive cases in which no diagnostic evidence can be obtained, either through skin testing or through a correlation of clinical manifestations. Dr. Donnally has told you about the various methods which are employed in treating the allergic food case and how elimination of the incriminating substance is accomplished. Mention

has been made of allergenically denatured foods. I have been particularly interested in this field and should like to add a few words.

Definition of Allergenically Denatured Foods

Dr. Ratner

By allergenic denaturation of foods, we have postulated that proteins which have become denatured as a result of exposure to high degrees of heat in the presence of water have lost their ability to shock animals previously sensitized.

Thus, lactalbumin obtained from raw milk and used as a sensitizing agent will sensitize the animal to raw milk, beef serum, dry milks, acidified milks, pasteurized milk, moderately cooked milk, butter, and cream. If thoroughly boiled milk (several hours) or freshly heated evaporated milk is used, no reaction will ensue. The shock-producing qualities are changed, and interestingly enough these heated foods have a higher coefficient of digestibility. They are more quickly broken down by enzymes than the raw foods. The sensitizing ability of heated foods is, therefore, also reduced.

We believe that the heat coagulates the soluble proteins temporarily, throwing them out of solution, but does not change the specificity or produce a true denaturation; and coupled with its ability to make the proteins more rapidly digestible, the heat makes them more readily broken down into harmless amino acids. Thus, the coagulated proteins are prevented from entering the blood stream through the permeable intestinal wall and are digested before they are capable of acting as a foreign protein, with the consequent production of allergic symptoms.

In general, it became clear from the studies of Ratner and Gruehl why dry milk, which is almost instantaneously dried on hot plates in the absence of water, should remain allergenic, whereas the albumin in evaporated milk, heated for twenty minutes at 116° C. in a sealed can in the presence of moisture, should become allergenically denatured. For example, it has been shown that dry crystalline egg albumin suffers no change by heating to 120° C. for five hours in a dry state, whereas moist egg albumin is quickly coagulated.

In the preparation of malt extracts very little heat is used in order to permit the optimum action of the malt enzymes, whereas dextrimaltose is superheated several times and filtered, and this procedure renders it nonallergenic.

And so with cereals, even when they are as complex as pablum, the high heating in the presence of water robs each of the ingredients of its allergenicity, whereas breads and crackers which are baked dry retain their allergenic properties.

Certain food proteins, such as casein, almond, oat, ovomucoid, soybean, and fish, appear to be resistant to moist heat. Fish and glue remain allergenic even though boiled. On the other hand, gelatin is so infrequently an offender, probably because it is boiled in its manufacture and is never consumed in the raw state.

I propose that the allergenically denatured diet can be used:

1. In all cases of allergy, irrespective of the sensitization.

2. During the newborn period.

3. As a basic part of the diet in infancy (always remembering to use cevitamic acid when the diet is used over prolonged periods).

4. During weaning from the breast.

5. During pregnancy and lactation when excessive amounts of foods are desired by the mother.

6. During convalescence from disease, pylorospasm, dysentery, chronic intestinal indigestion, and mucous colitis.

7. During malnutrition and chronic disease when large amounts of protein foods are added to the diet.

The following is a tentative list of allergenic and nonallergenic foods we have thus far worked out. Caution should be exercised, and for the time being, those foods which have been shown to be highly antigenic, even after cooking, should be kept out of the allergenically denatured diet, with the exception of casein which plays a minor role in the milk-sensitive case:

Allergenic Foods

Raw milk, casein
Milk boiled for a few minutes
Pasteurized milk
Acidified milk
Dry milk
Malted milks
Cream cheese, cottage, farmer
Cream sauces
Cream
Butter
Beef serum, rare meats
Eggs, raw, soft-boiled, coddled, fried, scrambled, and poached
All malt extracts
Malt brews
Malt sugar
Wheat, raw, white bread, rye, pumpernickel, ordinary toast
Pastries, pie crust, all cakes
Pancakes and waffles
Crackers, all cookies, pretzels, matzoth
Cooked corn meal, canned corn, corn on the cob, cornstarch pudding, corn bread
Rice and corn fritters
Oatmeal
Soybean
Fresh fruits and juices
All fresh vegetables
Condiments
Nuts
Confections
Chocolate
Fish

Allergenically Denatured Foods

Freshly heated evaporated milk
Freshly heated sma
Milk boiled for several hours
Freshly heated acidified evaporated milk
Thoroughly cooked beef and other meats
Beef broths and other meat broths and soups
Egg boiled for thirty minutes
Dextrimaltose
Corn syrup
Cane sugar
Thin melba toast
Precooked wheat
Prolonged cooked cereals
Spaghetti and macaroni cooked
Multiple precooked dry cereal (pablum, precooked corn cereals, popcorn)
Precooked rice cereals
Thoroughly cooked fruits, jams, and jellies
Thoroughly cooked vegetables

CHAIRMAN RATNER.—Dr. Hill will now say a few words on infant feeding in the first year in relation to food allergy.

Infant Feeding in the First Year in Relation to Allergy
Dr. Hill

In order to have a rational basis for infant feeding in its relation to allergy, it is first necessary to consider certain fundamental principles, which have been adequately covered by our chairman and Dr. Donnally.

Immune reactions, evidenced by precipitins in the blood and positive intracutaneous skin tests, take place, to be sure, indicating a transient phase of sensitization. This lasts for only a short time, and the individual develops no allergic symptoms. Thereafter, despite the fact that the protein of some foods is still absorbed unsplit,

as is the case with egg white for most persons, it is apparently inert. There has been developed a tolerance, or immunity, so that there is no longer produced any detectable reaction. This situation is to me a very interesting one; the individual is surely not the same as he was before he was exposed to the protein in question, for he has lost the power to react. This stage in the relations of any individual to foreign protein has been studied but little; it deserves more attention.

All persons do not react the same to the same stimulus when new protein is introduced. Because some are inherently different from the average run, possibly on account of hereditary make-up, possibly on account of other unknown variations, their stage of sensitization lasts longer, often many years, and is greatly exaggerated in intensity, and they develop abundant transferable antibodies and allergic symptoms. It is possible, however, for an infant with this type of constitution, who already may be sensitized to several foods, and who is having allergic symptoms from such sensitization, to develop a positive intracutaneous skin test to a new food and to have no allergic symptoms whatever from it, in the same way that the normal infant does.

It is likely that in persons of exactly the same reaction capacity, whether normal or abnormal, the amount of antigen absorbed and the time intervals between and the frequency of antigenic exposure may determine whether normal or abnormal, transitory or long-continued, sensitization is to take place. There are many variables and combinations of variables which determine the immunologic end result.

There are several animal investigations which are pertinent to the questions in hand. In the early days of anaphylaxis, Theobald Smith found that he could not shock guinea pigs who had been injected with small amounts of horse serum at frequent intervals. Richet later found that, if he fed egg daily to guinea pigs, they were shocked by injections of egg in inverse ratio to the number of days they had been eating it; thus, after three days of eating egg, 78 per cent could be shocked, after seventeen days, 25 per cent, and after forty-five days only 13 per cent. Wells found that guinea pigs raised on an oat-containing ration could not be sensitized or shocked with oat protein. Schloss found essentially the same thing for egg. Manwaring, more recently, found that he could easily sensitize dogs with horse serum if only one or two doses were given, but that if he gave twelve doses at four-day intervals, he could not shock them even with large doses. He says definitely that they had passed the stage of sensitization and had become immunized.

All this can be applied to the question of when and how to introduce new foods into the diet of an infant.

I am not entirely in sympathy with certain extremes at present fashionable in infant feeding. By this, I mean the practice of giving very large amounts of milk in concentrated form, and large amounts of cereal and vegetables, and heaven knows what else, at an early age. There is a happy medium in all things, and while I should by no means wish to return to what I was taught as a student twenty-five years ago—that cereal should not be given until 10 months, and vegetables not until 2 years—I think the pendulum has swung too far in the other direction. A young infant does not need a greatly varied diet, provided what he has is well balanced. Mothers are too eager to have their children progress rapidly; there is no sense in trying to make a child out of an infant, an adolescent out of a child, or an adult out of an adolescent.

I do not know whether food allergy is more common now than it was then; I am not even certain that it can be entirely prevented in susceptible infants by a more restricted diet, but there can be no question that, once out of the uterus, if an infant does not eat a food, he will not become sensitized to it. He must eat something, however, and I should not wish to advocate any foolish extremes in this or in any other matter connected with infant feeding.

I do think, however, that there is definite reason to believe certain things—that the younger the infant, the more likely are large amounts of undigested protein to pass through into the circulation, that large amounts are more likely to produce severe sensitization of long duration than small amounts, and that frequent and regular exposure is less likely to produce a severe sensitization and is more likely to produce final immunization than infrequent, intermittent exposure.

Milk sensitization is very common in eczematous infants. It is not often of high degree, however, and the fact that for a long time the infant has been taking regular amounts of milk every day is surely suggestive. The same holds true for wheat. Egg sensitization is still more common and frequently of very high degree, and until the baby is skin tested or has violent symptoms from eating a little egg at the age of 5 or 6 months, he has not been exposed to it for a relatively long time, either in utero, or through the breast milk in the early days of life. The breast-fed baby who goes into shock when he takes only a small amount of cow's milk is similar. Schloss mentions an infant who, early in life, was given egg albumin water for a diarrhea, with no untoward result. He did not receive any egg until several months later, when he reacted with violent symptoms. There is every reason to believe that he would not have had such a severe sensitization had egg been given every day after the first dose. I am sure, however, that sensitization is often produced by the daily taking of a food—milk and wheat sensitization bear witness to this—but I doubt that a severe sensitization to food is ever produced in this way.

There is undoubtedly a great difference in the sensitizing power of different foods, which depends probably, to a large extent, upon the fact that there is great variation in the digestibility of food proteins, and also that different proteins vary in their antigenic power. Egg, fish, and nuts stand at the top of the list.

With the foregoing facts as a basis, the practical measures which seem sensible and reasonably derived from the facts appear to me to be as follows:

1. Excessively large amounts of any food, including milk, should be avoided. Milk should be boiled.

2. New foods should not be introduced during or shortly after a digestive upset or diarrhea.

3. A more conservative attitude should be developed toward the practice of giving foods other than milk during the first few months.

4. A large variety of foods should not be given during the first year of life to an infant of an allergic family, or to one who is allergic himself.

5. Raw egg, either white or yolk, should be given to no infant. Hard-boiled egg yolk can be started at 5 or 6 months. It is probably best not to give whole egg until the child is 15 or 16 months old, and when it is given, the white should be well coagulated.

6. All new foods should be given regularly when once started.

CHAIRMAN RATNER.—Dr. Donnally will now say a few words about the diet in relation to the child from 2 years on.

Feeding After First Year in Relation to Allergy
Dr. Donnally

It is the first two years of life that constitute the most vulnerable period for the development of food allergy. Yet food allergies may develop beyond this period and may occur even in advanced age. I should like to discuss this subject, first, as it relates to normal persons, and, second, as it relates to the children whose mothers or fathers have frank manifestations of allergy, such as hay fever, asthma, urticaria, angioneurotic edema, gastrointestinal allergy, or other forms. In a consideration of both groups, the chairman's explanation of why heat allergenically denatures should be kept in mind. Heat coagulates the proteins, according to Ratner, without

denaturing them. Thus coagulated, their digestion is more easy and more readily accomplished, and their absorption through the intestinal walls as native proteins is prevented.

Normal children from 2 years of age on should avoid excesses, particularly of allergenically potent foods. Raw eggs and raw milk, raw meats, raw vegetables, fruits, and cereals should be carefully avoided, especially when the children are sick. The intestine is rendered more permeable by gastrointestinal diseases. There is scarcely a disease which a child may have that does not impair his capacity for digestion. The desirable way to feed a normal child is no food between meals, sufficient but moderate amounts of food at mealtimes, and cooked food when he is sick and afterward until his digestive capacity has been completely restored. When he eats a food which he has never eaten before, it should be eaten in small quantities, and it would be safer to cook it before consumption.

When we turn to the child of allergic parents or the child with infantile eczema, all that I have said about the feeding of the normal child applies to him with double force, as well as other precautions. He should have every new food which he eats cooked, and, furthermore, new foods should be added one at a time at intervals of not less than from three to seven days. Overeating is to be avoided in the potentially allergic child or the child with allergic manifestations.

DISCUSSION

CHAIRMAN RATNER.—We have presented some food for thought, and now the meeting is open to general discussion and questions which we will endeavor to clarify. Dr. Goldbloom, will you tell us some of your early experiences when you were associated with Dr. Holt?

DR. ALTON GOLDBLOOM, Montreal.—I want to take exception to Dr. Hill's statement that we have barely scratched the surface of allergy. What about the thousands of scratch tests performed? With relation to migraine versus abdominal pain, I am not familiar with its relation to allergy, but we do not see headaches in the child, whereas the history may reveal headaches in the mother, father, or perhaps an uncle. A careful family history may help in the case of a child difficult to handle, with vomiting, abdominal pain, etc. Lichen urticatus has interested me for many years. I have felt that there are two things associated with lichen urticatus in our part of the world, the season of ripening fruits—apples, etc.—and the reaction of chocolate and cocoa. Removal of these factors seems to relieve the condition in a week or ten days. Dr. Ratner referred to Dr. Holt's advice to boil eggs hard. I think this was done because of the ease in powdering them, rather than because he was attempting to make egg nonallergenic. Dr. Kerley, however, in those days boiled egg four hours. Schloss pointed out at that time that urticarias followed raw egg given during the convalescence following dysenteries. The practicing physician solves many problems by his common sense and smells out reasons for allergy in the child without any skin test or without any positive skin tests.

CHAIRMAN RATNER.—I think skin tests have tremendous value, as much as tuberculin tests. We think skin tests are here to stay despite the negative findings in so many cases.

It was asked how I determined the reduction in allergenicity of pablum and other cereals. It was done as follows: Guinea pigs were sensitized with extracts made from raw wheat, oat, corn, barley, yeast, etc. Three weeks later, specifically sensitized animals received an intravenous shock injection of an extract made from various cereals and breadstuffs and pablum, etc. If they did not react with anaphylactic shock, the test material was presumably denatured, for in each instance, the same animal received a subsequent injection of the raw extract to which it was sensitized and promptly developed anaphylactic shock. Hundreds of animals were used and were all carefully controlled.

DR. HILL.—The work of Dr. Ratner on denaturization of foods is important and must be accepted as true, but these guinea pigs experiences must not necessarily be translated to children. We must all try and see if we can help in this translation.

DR. DONNALLY.—Has anyone in the group here ever seen any symptoms which were, in your opinion, caused by pablum?

CHAIRMAN RATNER.—We have shown by experiments on guinea pigs that pablum is nonallergenic. It has been denaturized by heat.

DR. HILL.—Dr. Ratner has shown how foods can be denaturized. The work is excellent and the principle sound, but it is not 100 per cent dependable.

CHAIRMAN RATNER.—If you stick to all thoroughly cooked food, you are doing about as well as can be done. Always look for other factors in cases of allergy.

CHAIRMAN RATNER.—A vitamin C deficiency may cause a liability to allergy.

DR. HILL.—Relative to the vitamin question, we know nothing about the vitamins in allergy.

DR. JOHN J. POLLACK, Detroit.—I have had three cases in which arrowroot in the form of Royal Pudding has caused hives.

CHAIRMAN RATNER.—Eggs could explain that.

DR. HILL.—I don't see any reason why arrowroot couldn't be allergenic as well as anything else.

DR. E. P. RUSSELL, Berwyn, Ill.—I have had two or three cases of eczema in early infancy which were due to dextrimaltose. They cleared up when dexin was used and recurred when pablum was given. Sobee has a useful place but should be used in special cases. Local treatment is often far more important than food changes. Dermatologic diagnosis should be more carefully made.

CHAIRMAN RATNER.—I do not believe that dextrimaltose can produce reactions. There is no protein in it. It is absolutely nonallergenic. It is just as nonallergenic as water, that is, pure water.

DR. J. D. CRAIG, New York.—Do you see any other type of skin rash outside of urticaria and eczema due to foods? Patients sometimes have a roseola after some foods.

DR. HILL.—Allergen antibodies react in the skin, causing dilation of the superficial vessels. First, an erythema, and if it goes on further, an exudation of cells, may occur and papules are formed; if it goes further, a transudation of serum with vesicle formation occurs, and you may call it eczema. We may see all sorts of reactions, as you have suggested.

DR. DONNALLY.—Drugs may be a factor in some of these cases.

CHAIRMAN RATNER.—I think Dr. Hill's answer very excellent.

DR. HARMON TREMAINE, Boise, Idaho.—Why are there phases when the infant is very allergic, and at other times not? During teething, he may have symptoms suggesting an increased vulnerability.

CHAIRMAN RATNER.—Yes, an increased permeability may occur at those periods. During teething, a general irritability of the infant is present and may result in increased scratching.

DR. HILL.—There is a great difference in the ease with which children can be sensitized.

DR. S. D. GIFFEN, Toledo.—What is the difference between allergic and nonallergic tissue?

CHAIRMAN RATNER.—Allergic tissues have fixed antibodies in them and react when the specific allergenic substance comes in contact with the antibodies fixed in the tissue. The irritation thus produced results in a spasm and edema.

DR. M. ADELMAN, Providence, R. I.—Has any work been done to determine the sensitivity of tissues isolated from the sympathetic nervous system?

CHAIRMAN RATNER.—Yes, on uterine muscle suspended in Locke's solution, the classical Dale experiment.

Dr. Hill, will you elaborate upon cases having intestinal allergy, but negative skin tests?

DR. HILL.—I have had only a few cases. They are certainly not very common, but they do occur.

DR. DONNALLY.—I believe such cases do occur, but I have had very little experience with them. There is usually some slight skin reaction.

CHAIRMAN RATNER.—In the cases of identical twins whom I studied, one had urticaria, and the other, gastrointestinal disturbances. I assume, therefore, that the one with gastrointestinal symptoms was as sensitive as the one with urticaria, but had no skin reactions.

DR. BANICE FEINBERG, Providence, R. I.—What relation to eczema do the endocrines have?

CHAIRMAN RATNER.—Probably only a secondary effect. Some children have delayed ossification and a low metabolic rate. Eczema in this type of child is helped by giving thyroid.

DR. J. GLASER, Rochester, N. Y.—We have made basal metabolic determinations on allergic children. On some we used thyroid and noted improvement. One patient with a vasomotor rhinitis and a −35 metabolic rate recovered with thyroid.

DR. C. O. TERRELL, Fort Worth.—What became of the idea of the unsaturated iodine factor in fats as a cause of eczema?

CHAIRMAN RATNER.—We have used the unsaturated iodine fats to some extent. There is some truth in the theory.

DR. DONALD C. MEBANE, Toledo.—Does the amount of fluid given have any influence? What about the use of potassium instead of sodium? The lay public seems to be very much impressed by the idea.

CHAIRMAN RATNER.—Sodium salt may increase the edema, but potassium salt should not be used. It may produce nausea and is a dangerous drug.

DR. H. A. SLESINGER, Windber, Pa.—Is there any authentic work on the use of histamine in desensitization in chronic urticaria?

DR. GIFFEN.—Histaminase, an extract of intestinal glands, counteracts histamine. It seems to help eczema. I have used it in about six cases to prevent immune reactions.

DR. GLASER.—We have used histaminase (Winthrop) put up in enteric-coated capsules. We have had no results in hay fever or eczema.

DR. HILL.—Regarding papular urticaria, I don't know anything about it at all. It is very hard to distinguish from insect bites. The dermatologists know that at times raw fruits cause it. An Englishman studied 270 cases and could get nothing out of his skin tests, nor could he find any greater incidence in the families. Walzer found a high incidence of allergy in the family. An Englishman thought it might be due to the house environment, dusts, etc. Even though the patients reacted negatively to skin tests, they improved when put in a hospital.

CHAIRMAN RATNER.—I don't accept it as a strictly allergic problem.

DR. GORDON MANACE, Toronto.—I have had three cases of papular urticaria recently, and I had a lot of trouble differentiating them from insect bites. Scratching makes it hard to distinguish from bites, and the condition continues over a week.

DR. HILL.—Papular urticaria does not result in an eosinophilia. The French and the German authors write about prurigo, ferox and malix; it seems that our papular

urticaria is a mild prurigo. The chances are that it should not be called urticaria, but allergy.

CHAIRMAN RATNER.—I want to remind you that acid salves should be used rather than those that are alkaline in reaction.

DR. ALFRED S. TRAISMAN, Chicago.—Papular urticaria is self-limited. It runs a certain course and disappears without treatment.

DR. HILL.—I do not believe that papular urticaria is allergic in all cases. Does recurrent vomiting in early childhood become migraine later in life?

DR. H. HOSEN, Port Arthur, Texas.—Many so-called migraine cases are allergic noses with obstructed sinuses, and shrinking relieves them. I have found that the cases with little discharge have more headaches, and conversely, the more discharge, the less headache.

DR. MANACE.—The majority of my allergies are eczema, and I was interested in the discussion about the skin tests. I rarely skin test in eczema but follow the same routine as in my normal patients. I have not found that pablum or vegetables are allergenic. I try to get the confidence of the mother and tell her that the eczema is going to subside eventually. My skin tests were negative in my food tests, and I lost interest in food testing.

DR. DANIEL B. LANDAU, Hannibal, Mo.—I wonder if the quality of our extracts is standard; often some of our food extracts do not give reactions at all. Some staple ones, such as egg, milk, etc., are dependable, because we get so many negative reactions when using them.

DR. DONNALLY.—It is comparatively infrequent in children to obtain a positive skin test. Slight reactions are frequently obtained every time they have eaten bacon, and the skin test for pork was negative. This extract question is vital. They must be potent.

CHAIRMAN RATNER.—In relation to potent extracts, I do not believe in intracutaneous tests as a rule. Three children died last year due to such a method of testing. Scratch tests must be emphasized in the practice of pediatrics. Vaughan states that 50 per cent of their intracutaneous tests are nonspecific. Schloss did all of his monumental work with the scratch test alone.

DR. HILL.—I agree with Dr. Ratner, relative to scratch tests as a routine in children. On the other hand, if they are used alone, you will miss some important cases. I have never tested for egg intradermally. In milk scratch tests, one will miss many reactions, as in dust, kapok, and some pollens which have even been tested with a 1:500 dilution before showing a positive reaction.

DR. DONNALLY.—It is a frequent thing to get a positive skin test of no clinical significance, as brought out by Dr. Hill earlier today. We should stress the fact that food allergy is comparatively infrequent and that inhalants are more usually the offenders.

DR. SAMUEL P. WAINWRIGHT, Birmingham, Ala.—Will you discuss the relative merits of dermal and intradermal tests and the reading of these tests with ultraviolet light? In boiling milk, what difference is there between the so-called three minute and that double boiled for thirty minutes? Are homogenized foods contraindicated, and is their absorption rate increased, making them more likely to be allergenic? What about the red reaction around some areas? I am referring to small areas on the body of an infant just a few days old that somewhat resemble mosquito bites. Does the smelling of some foods produce an allergic effect? Lastly, what is the first sign of allergy that may be observed in an infant?

CHAIRMAN RATNER.—It is a startling thing to find that 50 per cent of the children who are sensitive to food are also sensitive to external factors. Three-minute boiling and thirty-minute boiling are no good at all; evaporated milk is

denatured. All food must cook from three to four hours in water. Homogenized vegetables may be a problem.

DR. HOSEN.—Why does water aggravate the symptoms in eczema, and what percentage can be relieved by food and contact elimination?

CHAIRMAN RATNER.—Water is highly irritating in eczema, but I do use a bland soap and water to clean up a long-standing case. As to contacts, we are all pediatricians and must keep all factors in our minds at all times—foods, contact, and metabolic causes.

DR. JOSEPH YAMPOLSKY, Atlanta, Ga.—Does early administration of cod-liver oil cause allergy, and should we use crystallized vitamins instead?

CHAIRMAN RATNER.—I spoke to Dr. Cox of Mead Johnson & Co., and he assured me there is no protein in it as they make it. I think we should use cod-liver oil. It is better than the crystalline products which are a passing phase. Stick to concentrated brewer's yeast.

DR. DONNALLY.—I do not approve of our vitamin mixtures. They haven't been established as beneficial. There are exceptional cases, however, such as nausea, etc., which might warrant their use.

CHAIRMAN RATNER.—Rickets developed in patients at a large city hospital due to inefficient cod-liver oil furnished by the city. We must use reliable cod-liver oil. I like to stick to cod-liver oil for the unsaturated fatty acids may be of some value.

DR. HILL.—Personally, I cannot recall an eczema due to a fish oil, but I take my patients off of it just the same if they have allergic manifestations. A doctor in Philadelphia in the government service found out that people who were sensitive to cottonseed could ingest cottonseed oil without symptoms.

DR. WAINWRIGHT.—Relative to sensitization to sugars, does adding malt to correct constipation effect a change in symptoms due to a transient allergic reaction? In the spring and summer, when children are eating freely of fruits and vegetables, melons, berries, etc., is it possible that the diarrheas are due to allergy?

CHAIRMAN RATNER.—Diarrhea is not necessarily allergic in origin, as emphasized by Dr. Hill, but we may get loose stools in allergy. Crude sugars and malt extracts are allergens. Purified sugars such as dextrimaltose, cane sugar, lactose, and corn syrup are nonallergenic. I note that Dr. Lyon is in the audience, and I should like to ask him to recite a case of his that I regard as the earliest reported case of food allergy.

DR. GEORGE M. LYON, Huntington, W. Va.—I wish to report the case of an infant 3 weeks of age. When first seen he had an erysipelas-like eruption which proved to be angioneurotic edema and urticaria. Adrenalin caused the edema to disappear.

The only food that the baby had had was breast milk. Skin tests were tried, and the baby was found to be sensitive to navy bean, corn, and his mother's milk. The eruption could be controlled by keeping the baby off the breast milk.

Inquiry showed that the mother had nothing but corn and beans to eat during the greater part of her pregnancy, with a little milk occasionally. I have come to no conclusion as to how the baby was sensitized, but at Dr. Ratner's request I am reporting the case.

CHAIRMAN RATNER.—I believe that Lyon's case is supportive evidence for my concept that excessive indulgence in certain foods during pregnancy may at times sensitize the fetus in utero. It seems doubtful that the infant could have been sensitized in so short a time from the minute amounts of foreign protein in the breast milk. The more plausible explanation, it seems to me, is that the infant was sensitized in utero.

Dr. Glaser, will you tell some of your experiences with food allergy?

DR. GLASER.—I agree with Dr. Hill that cyclic vomiting is not commonly allergic. Recurring abdominal pain is usually not of an allergic etiology. Careful study of the individual cases will, as a rule, determine other causes for the pains of this type.

It was stated that jello was not allergenic. Might this not be due to the chemical constitution of jello rather than to the effect of heat? Macaroni was also mentioned as nonallergenic. Perhaps the fact that it is made from durum wheat may be the factor.

Pablum, I have found, very rarely causes allergic reactions.

Rorbach observed that certain skin diseases resembling eczema could be cured by changing diets, but all eczema does not respond to dietetic changes. The use of evaporated milk may help some children, but it certainly does not help all of them. Some are not affected by the elimination of any foods.

I believe, however, that it is well to try dietary changes and eliminate possible environmental factors before skin testing. In adults, asthma, hay fever, and urticaria are the common allergic manifestations. In infants, colic, eczema, and recurrent upper respiratory infections are the most common allergic symptoms. The fundamental factors in the allergic response are edema and spasm of smooth muscle; the latter follows the first.

The presumptive reasons why colic may be allergic are:

1. Colic develops at about 3 weeks of age. This corresponds to the time necessary for the development of allergic reaction.

2. As new foods are added to the diet, precipitins appear, and these disappear when tolerance is established. Skin tests respond in similar manner.

3. More allergic than nonallergic infants have colic.

CHAIRMAN RATNER.—I do not believe that the absence of the aromatic amino acid group explains the nonallergenic nature of jello; I think it is due to the heating used in its preparation. Durum wheat may be the explanation for the fact that macaroni is seldom allergic in effect, as it is a resistant hard form of wheat, but I am not sure.

I would like to discuss the question of the effect of heat upon the allergenic factor in milk. Evaporated milk is definitely less allergenic than unheated milk. It has been stated that some eczema cases do not clear up when evaporated milk is substituted for other milk. This may be true, but since about 50 per cent of these babies are sensitive to outside factors, evaporated milk cannot be blamed for the failure of these cases to clear up until, at least, these other factors have been eliminated. There have been some cases of casein sensitivity reported. Dr. Schloss has reported three or four cases, and I have seen one or two.

DR. HILL.—In regard to evaporated milk, it is only fair to state that it is less allergenic than ordinary milk. Children who are extremely sensitive to milk cannot take even evaporated milk.

In eczema there are so many etiological factors that it is hard to draw any bona fide conclusions as to results of any treatment. If the eczema is due to milk, it can be cured by a milk-free diet.

I have repeatedly seen eczema return when evaporated milk was given in such cases. A few respond favorably to goat's milk, but cross reactions prevent such action in many others.

If cow's milk must be fed, evaporated milk is probably the best form.

Casein is of less importance than lactalbumin in most cases. Pure casein will give skin reactions, but it is difficult to make pure casein. A paper will soon be published showing that casein sensitivity is relatively common as a cause of eczema. It is not

very common to have a double allergic reaction to casein and lactalbumin. Possibly lactalbumin is not rendered nonallergenic in evaporated milk.

I have seen babies who nearly die because they were so sensitive to the species-specific factor in cow's milk. These may not react to goat's milk. Eczema is the result of the reaction to either the species-specific factor or to certain nonspecific protein factors.

CHAIRMAN RATNER.—Dr. Hill, why make the milk problem so complex? There are few cases of casein sensitization. It is almost impossible to get pure casein, so why argue about it until casein can be purified? All your experiments to the contrary will not convince me until you can purify casein. As we have shown, all caseins cross react with lactalbumin, and, conversely, lactalbumin with casein. Lactalbumin is the soluble fraction that escapes digestion, whereas casein is only relatively soluble and is precipitated by rennet and HCl. Arguing from clinical experience against controlled laboratory experiments seems hazardous.

It is the coagulation of the lactalbumin which lessens its allergenic nature. Evaporated milk will give results in the overwhelming majority of cases, providing other factors are not responsible. Haven't you agreed that very few cases are sensitive to milk alone?

Dr. Hill, at your round table discussion two years ago, didn't the majority feel that they had obtained good results with evaporated milk?

DR. HILL.—That is my recollection.

DR. MEBANE.—It is impossible to get good results with evaporated milk in the overwhelming majority of cases of eczema.

CHAIRMAN RATNER.—Eczema is improved but not cured without considering other factors. Local treatment and environmental and other general phases must be taken into account.

DR. HILL.—Allergy is one of the most complicated things I know. It cannot be made as simple as Dr. Ratner indicated; there are too many factors which are unknown.

CHAIRMAN RATNER.—That is true, as I have repeatedly stated, but the milk phase of it is simple. Just use heated evaporated milk and then concentrate on the other factors, but don't waste time flitting about from evaporated to goat's milk to cemac, to sobee. Stick to evaporated milk, and concentrate on the judicious use of local therapy, environmental factors, other sensitivities, and thyroid when indicated.

DR. HILL.—A great many cases of eczema cannot be cured. There are cases of erythrodermia in which no treatment does any good. They usually recover in time. There are cases of atopic eczema which are sensitive to so many things that nothing helps. Perhaps if they were put in a glass case away from everything, they might keep well. Some cases do well on sobee. I really use evaporated milk in most cases. It is foolish to take every baby off milk. Treat them with local treatment; cases of erythrodermia improve most on use of sobee.

CHAIRMAN RATNER.—Salt-free diet helps some by causing dehydration.

DR. DWIGHT A. WEIR, Mansfield, Ohio.—What is the difference between evaporated milk and whole milk boiled ten minutes?

CHAIRMAN RATNER.—The lactalbumin is not sufficiently coagulated in the latter.

DR. WEIR.—Does the emulsification of the fat have any effect?

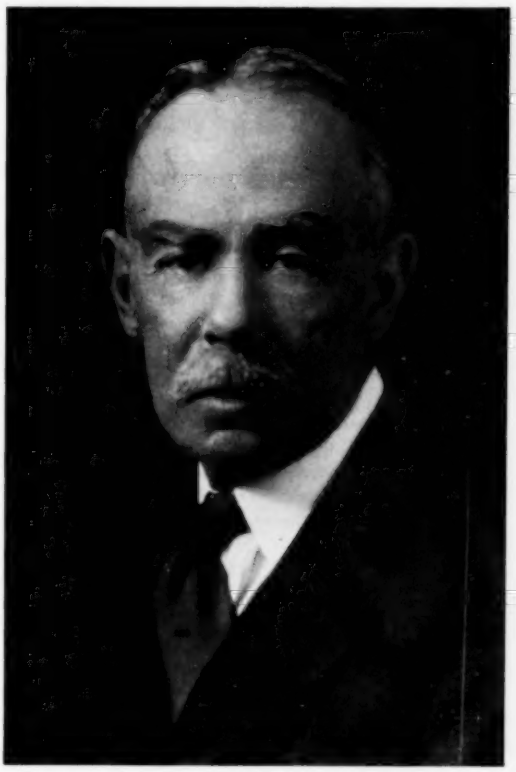
CHAIRMAN RATNER.—Homogenization makes it easier to digest the fat and the protein because of the greater molecular surface exposed to the digestive juices. Homogenization also produces a soft curd.

I hope that we have all learned something and I believe that in attempting to clarify this complex subject, Hill, Donnally, and I have learned as much as you have. We thank you for a very pleasant and stimulating discussion.

In Memoriam

JOHN LOVETT MORSE

In the death of John Lovett Morse on April 2 American pediatrics lost one of its most distinguished and well-known leaders. He was born in 1865, and April 21 would have been his seventy-fifth birthday. He was a founder of the Academy of Pediatrics and its second president serving from 1931 to 1932.



JOHN LOVETT MORSE
1865-1940

He was born at Taunton, Mass., the son of Erastus and Sarah Seabury Bassett Morse. After graduation from Harvard College in 1887 he attended Harvard Medical School from which he was graduated with the M.D. degree in 1891. After a year and a half of internship at the Boston City Hospital he started practice. The first few years found him doing orthopedic work at the Children's Hospital, working in the neurological clinic of the Boston Dispensary and serving at the Lying-In Hospital. In 1896 he was appointed assistant in clinical medicine at Harvard Medical School.

Four years later in 1900, he turned definitely to pediatrics and became instructor in the diseases of children at Harvard. In 1906 he was appointed assistant professor, in 1911 associate professor, and in 1915 professor of pediatrics. In 1921 he became professor emeritus. For many years he served as chief of the medical staff of the Children's Hospital and Infants' Hospital, as well as consulting pediatrician to other Boston institutions.

In addition to membership in his local and regional medical and pediatric societies, Dr. Morse throughout his life was active in the national pediatric organizations. He was elected to the American Pediatric Society in 1896, served on its Council from 1904 to 1911, and was president in 1913. The proceedings of the Society contain many papers which he presented and discussions in which he took part. He was one of the early applicants for certification by the American Board of Pediatrics and held certificate No. 1 by vote of the Board.

Dr. Morse was an active contributor to pediatric literature, and his bibliography includes nearly 300 items. The first article in the first issue of THE JOURNAL OF PEDIATRICS (July, 1932) was his address as President of the Academy for that year. One of his last contributions, written when he was nearly seventy, "Recollections and Reflections on Forty-Five Years of Artificial Infant Feeding," an article of important historical value, appeared in the JOURNAL in September, 1935. In 1911 he published a volume, *Case Histories in Pediatrics.* He was coauthor, with Dr. F. B. Talbot, of *Diseases of Nutrition and Infant Feeding,* and, with Drs. E. T. Wyman and L. W. Hill, of *The Infant and Young Child.*

In 1906 he married Adelaide M. Fairbrother of Portland, Maine, who with a son, Lovett Morse, survives him.

Dr. Morse was one of the leaders in an important period in the development of pediatrics in America. Entering pediatrics from general practice as was the custom previous to 1910, he was among the first to limit his work to children. In keeping with the knowledge of that period his approach was distinctly clinical, and he developed an acumen and skill which brought him a widespread reputation. He remained throughout his life a clinician, and he had little interest in pediatrics outside the diagnosis and treatment of sick children. He gave much of his time to teaching and hospital work and here again, as exemplified by his text, *Case Histories,* his interest and approach was clinical.

He had a vivid positive personality. He was tenacious in his viewpoints and opinions. He was loyal to his friends and persistent in his dislikes. He had a sharp, at times even caustic, way of speech which enlivened many a meeting and discussion. There was no hesitancy in the expression of his viewpoints and adherence to what he felt and thought was right. To the present-day "older generation" of pediatricians he will always remain a distinct unforgettable figure, liked and respected for the work he did and the deserved position he made for himself during the days when pediatrics in America was developing into a special field of medical practice.

Academy News

Dr. Glen B. Cullen, Professor of Pediatric Research at the University of Cincinnati and Director of Laboratories, Children's Hospital Research Foundation since 1931, died April 11 of coronary occlusion. He was fifty years of age at the time of his death.

Dr. Cullen studied chemistry at the University of Michigan, receiving the degree of B. Chem. Eng. in 1913. He then became Research Chemist at the Rockefeller Institute where he worked until 1922. During this time he received his Ph.D. from Columbia in 1917. After two years as associate Professor in Research Medicine at the University of Pennsylvania, he was appointed Professor of Biochemistry at Vanderbilt University in 1924, remaining there until 1931, when he became associated with the Department of Pediatrics at the University of Cincinnati. He was a member and past president of the American Association of Biologic Chemists and of the Society for Experimental Medicine and Biology. Since turning to the field of pediatric research, he had been elected to membership in the American Pediatric Society, the American Academy of Pediatrics, and the Society for Pediatric Research.

Dr. Bernard Fantus, Chicago, Ill., Associate member of the Academy, died April 14.

Book Reviews

Directory of Medical Specialists. Compiled by the Advisory Board for Medical Specialists, New York, 1939, Columbia University Press. Pp. 1573. Price $5.

The first edition of the directory of specialists holding certificates of the various Specialty Boards was published in March, 1940, the date of the publication having been delayed to include all licentiates of 1939. After a short section on the composition and functions of the Advisory Board, a chapter is given over to each of the 14 boards. Each contains a biographical list of the licentiates of the particular specialty arranged in alphabetical order by state and city. The data for each licentiate include, in addition to name and address, date of birth, medical school, year of certification, hospital appointments, teaching positions, and society memberships. This occupies some 1,200 pages. The final section contains an alphabetical list of the 14,338 physicians holding certificates with address and designation of specialty.

The format of the book is excellent and the type clear and of a size to be read easily without eyestrain. It is planned to publish a new edition every two years. The directory fills a long felt need.

Essentials of the Diagnostic Examination. John B. Youmans, M.D., Associate Professor of Medicine and Director Postgraduate Instruction, Vanderbilt University Medical School. New York, The Commonwealth Fund, 1940. Pp. 417. Price $3.

From his experience in teaching "practitioners" diagnostic and laboratory methods, Dr. Youmans has collected in a handy small volume all of the diagnostic methods needed in general practice and available to all physicians. The first and second chapters are given over to the history and physical examination. Part II consists of laboratory tests—blood, urine, sputum, feces, etc.—which may be easily carried out by the physicinn in a simple office laboratory. The author gives but one method for each examination which has been selected on the basis of reliability and general applicability. An appendix with lists of necessary laboratory supplies, requisites, etc., is added. The book does not take the place, as the author points out, of the larger texts on physical diagnosis and laboratory methods used in undergraduate teaching. To these, the author frequently refers. The format is excellent with numerous tables and four excellent colored plates of the blood. The book would seem to fulfill exactly the purpose for which it was written and intended, that is, a simple accurate discussion of the physical examination and of laboratory tests which can and should be carried out by the general practitioner in his diagnosis.

As the Twig Is Bent. Leslie B. Hohman, M.D., The Macmillan Company, New York, 1940, pp. 291. Price $2.50.

Another addition to the rapidly increasing list of books on the problems of childhood and child guidance for the parents, its contents are divided into 26 brief chapters written in a nontechnical nondidactic way which should be intelligible to better educated readers. A few of the chapter headings will give a rough oversight of the contents and style: "Control Your Child for Happiness," "Spank—If You Must," "Ultramodern Education, Movies, Radio, and Other

Excitements," "Sweet Sixteen and—." The book is really much better than these chapter headings might indicate. Dr. Hohman has had a wide experience, and he draws upon it freely. The reviewer feels what he has written is sane and sound, although it will seem in some places as outmoded to the "ultramodern." It belongs decidedly in the upper part of the list of books which can be recommended for parents. If there is any particular fault, it lies perhaps in unconsciously creating the impression that everything a child does is potentially a problem, and in not sufficiently emphasizing the importance of the conflict as a necessary process in the development of character. A widespread reading of the chapter, "Ultramodern Education," would help a lot.

Cancer in Childhood. Edited by Harold W. Dargeon. St. Louis, 1940, The C. V. Mosby Company. Pp. 114. Price $3.

The papers from the Memorial Hospital for Cancer and Allied Diseases in New York which were published as a symposium in THE JOURNAL OF PEDIATRICS for September, 1939, have been reprinted in this volume. To the original eight papers by Dargeon, Coley and Peterson (Bone), Craver (Lymphatic System), Dean (Genitourinary Tract), Kelly (Gynecologic), Martin (Cancer of the Head and Neck), Pack and Anglem (Soft Tissues), and Watson (Blood and Lymph Vessels) a chapter, "A Survey of Cancer in Childhood," by D. James Ewing, Director, Memorial Hospital, has been added. The papers are particularly important as they represent a large group of children studied in one of the foremost cancer hospitals in the world. Despite a decrease in the number of individuals under 16 years of age between 1920 and 1936, there was an increase of deaths from cancer from 609 in 1920, to 982 in 1936. An index has been included.

Congenital Malformations. A Study of Parental Characteristics With Special Reference to the Reproductive Process. Douglas P. Murphy, M.D., Philadelphia, 1940, University of Pennsylvania Press. Pp. 99. Price $2.

A detailed study of the family background and environment of 890 babies born with congenital malformations was made. Data as to frequency of malformation, relationship to race, economic status, health and age of the parents, the conception rate, order of pregnancy, diet of mother, health during pregnancy, etc., were obtained and analyzed. The observations lend in general to the conclusion that malformations arise solely from influences which affect the germ cells prior to conception. It is one of the most complete studies on congenital malformations which has been made.

The Physical and Mental Growth of Girls and Boys Age Six to Nineteen in Relation to Size and Maximum Growth. Frank B. Shuttleworth. Monographs of the Society for Research in Child Development. Vol. IV, Serial No. 22, Number 3, 1939.

Motor Performance in Adolescence. Anna Espenschade. Ibid. Vol. V, Serial No. 24, Number 1, 1940.

These are two further monographs in the important series being published by the Society for Research in Child Development. Dr. Shuttleworth has analyzed the data obtained by the Harvard Growth Study as related to the matter of growth. The material has been charted into over 150 graphs. Dr. Espenschade presents the study of motor performance made at the University of California Institute of Child Welfare during the years 1934-1938. As with all of this series, the material is presented largely by means of excellent graphs.

Chemotherapy and Serum Therapy of Pneumonia. Frederick T. Lord, M.D., Elliot S. Robinson, M.D., and Roderick Heffron, M.D., New York, 1940. The Commonwealth Fund. Pp. 174. Price $1.

The development of chemotherapy in the last two years has necessitated the publication of this third monograph to replace the previous ones published by the Commonwealth Fund. The subjects of typing, use of chemotherapeutic agents, serum, relative merits of the two, combined use, together with a discussion of choice and contraindications, are presented in a clear and concise way. The book is essentially practical and is a splendid presentation of the present status of pneumonia therapy.